Non-invasive reservoir pressure parameters:

measurement and clinical relevance

By

Xiaoqing Peng

BPharm, MPharm

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

July 2018

Menzies Institute for Medical Research

College of Health and Medicine

University of Tasmania

Hobart, Tasmania, Australia

Declarations by Author

Originality

This thesis contains no material which has been accepted for a degree or diploma by the University of Tasmania or any other institution, except by way of background information and duly acknowledged in the thesis. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright. I have also acknowledged, where appropriate, the specific contributions made by co-authors of published and submitted manuscripts.

Authority of Access

The publishers of the manuscripts comprising chapters 2, 3, and Appendix 1 hold the copyright for that content, and access to the material should be sought from the respective journals. This thesis is not to be made available for loan or copying for two years following the date this statement was signed. Following that time, the remaining non-published content of the thesis may be made available for loan and limited copying and communication in accordance with the Copyright Act 1968.

Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, and full ethical approval from the relevant institutions was obtained for all studies outlined in this thesis. All individual participants provided written informed consent for involvement in the respective research studies.

Xiaoqing Peng
June 2018

Statement of Co-author Contributions to Papers Contained within this Thesis

Chapter 2

Peng X, Schultz MG, Picone DS, Black JA, Dwyer N, Roberts-Thomson P, Davies JE, and Sharman JE. Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper-arm. *Journal of Hypertension*. 2017 Sep;35(9):1825-1831.

Author contributions: XP: performed experiments, analysis and interpretation of data and drafted manuscript; MGS: project conception and study design, interpretation of data, drafted manuscript and critical revision of manuscript; DSP, JAB, ND and PR: performed experiments and critical revision of manuscript; JED: interpretation of data and critical revision of manuscript; JES: project conception and study design, interpretation of data and critical revision of manuscript.

Chapter 3

Peng X, Schultz MG, Abhayaratna WP, Stowasser M, Sharman JE. Comparison of central blood pressure estimated by a cuff-based device with radial tonometry. *American Journal of Hypertension.* 2016 Oct;29(10):1173-8.

Author contributions: XP: analysis and interpretation of data, drafted manuscript; MGS: interpretation of data, critical revision of manuscript; WPA and MS project conception and study design, critical revision of manuscript; JES project conception and study design, interpretation of data, critical revision of manuscript.

Chapter 4

Peng X, Schultz MG, Picone DS, Dwyer N, Black JA, Roberts-Thomson P, Sharman JE. Non-invasive measurement of reservoir pressure parameters from brachial-blood pressure waveforms. *Journal of Clinical Hypertension.* 2018 Dec:20(12):1703-1711.

Author contributions: XP: performed experiments, analysis and interpretation of data and drafted manuscript; MGS: project conception and study design, interpretation of data and critical revision of manuscript; DSP, ND, JAB and PR: performed experiments and critical revision of manuscript; JES: project conception and study design, interpretation of data and critical revision of manuscript.

Chapter 5

Peng X, Schultz MG, Wake M, Mynard J, Cheung M, Otahal P, Burgner D, Ellul S, Liu R, Juonala M, Sharman JE. Association of brachial-cuff excess pressure with carotid intima-media thickness in Australian adults: a cross-sectional study. Fully drafted and under co-authors' review.

Author contributions: XP: contributed to data collection, analysis and interpretation of data and drafted manuscript; MGS and JES: project conception and study design, interpretation of data and critical revision of manuscript; MC, MW and DB, project conception and critical revision of manuscript; JM: suggestion of data analysis and critical revision of manuscript; PO and SE: statistical assistance and critical revision of manuscript; RL: contributed to data collection and suggestion of data analysis.

We, the undersigned agree with the above stated contributions for each of the above published (or submitted) peer-reviewed manuscripts contained within this thesis:

Professor James Sharman

Primary candidate supervisor

Menzies Institute for Medical Research

College of Health and Medicine

University of Tasmania

Date: 31-01-2019

Professor Alison Venn

Head of School,

Menzies Institute for Medical Research

College of Health and Medicine

University of Tasmania

Date: 01-02-2019

Additional publications contributed to during candidature but do not form part of the thesis

Picone DS, Schultz MG, Otahal P…**Peng X**… et al. Accuracy of cuff measured blood pressure: compendium of three separate systematic reviews and individual participant data meta-analyses. *J Am Coll Cardiol.2017 Aug; 70 (5): 572-586.*

Picone DS, Schultz MG, **Peng X** et al. Discovery of new blood pressure phenotypes and relation to accuracy of cuff devices used in daily clinical practice. *Hypertension. 2018 Jun;71(6):1239-1247.*

Picone DS, Schultz MG, **Peng X**, Black JA, Dwyer N, Roberts-Thomson P, Sharman JE. The best calibration methods to estimate aortic blood pressure. *Journal of Hypertension. 2019 Feb;37(2):307-315.*

Abstracts and Presentations at Scientific Conferences that relate to this Thesis

Peng X, Schultz MG, Picone DS, Black JA, Dwyer N, Roberts-Thomson P, Davies JE, and Sharman JE. Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper-arm. Oral Presentation, Arterial Hemodynamics, London, UK, June 2016

Peng X, Schultz MG, Abhayaratna WP, Stowasser M, Sharman JE. Comparison of central blood pressure estimated by a cuff-based device with radial tonometry. Poster presentation, High Blood Pressure Research Council of Australia, Melbourne, Australia, December 2015

Peng X, Schultz MG, Picone DS, Dwyer N, Black JA, Roberts-Thomson P, Sharman JE. Non-invasive measurement of reservoir pressure parameters from cuff blood pressure waveforms. Moderated poster, awarded the Outstanding Presenter, Seoul, South Korea, September 2016

Peng X, Schultz MG, Wake M, Mynard J, Cheung M, Otahal P, Burgner D, Ellul S, Liu R, Juonala M, Sharman JE. Brachial cuff reservoir pressure parameters are associated with end-organ markers of cardiovascular risk in Australian adults: a cross-sectional study. Oral presentation, International Society of Hypertension, Beijing, China, September 2018.

Acknowledgements

It is my great honour to work with and learn from brilliant academics at a world-class institute, the Menzies Institute for Medical Research. This PhD would not have been completed without the guidance and assistance of a number of people to whom I would like to specifically acknowledge.

First, I wish to sincerely thank my primary PhD supervisor, Professor James Sharman, for providing me with the opportunity to work on this promising programme of research. His patient guidance, constructive suggestions and enthusiastic encouragement have helped me develop as a research fellow. His belief in and enthusiasm towards scientific research will inspire me throughout my entire career. I would also like to thank him for teaching me communication skills and the attitude to life.

I would like to express my great appreciation to my secondary supervisor, Doctor Martin Schultz, for teaching me the skills of data collection, data processing, and manuscript writing since the beginning of my PhD. I also would like to thank Doctor Dean Picone for sharing his research experience with me and for providing invaluable suggestions on my studies.

I am grateful to have been surrounded by the inspiring and supportive members of the Blood Pressure Research Group (Penny, Matt, Niamh, Myles, ZhengZheng, Ricardo, Adam, Sonja, Rachel, Ella, Paul, Greta, and Erin). I owe thanks to Professor Kim Park for generously sharing his knowledge of the reservoir-excess pressure model. I also would like to thank Doctor Xun Yang, for providing assistance with the Matlab programme, and Guoqi Cai, for his generous statistical advice.

Many thanks to the clinicians in the catheterization laboratory at Royal Hobart Hospital and to the CheckPoint team at Murdoch Children's Institute. It was enjoyable to work with these

people to collect data for the studies presented in this thesis. I must extend thanks to all of our participants, who are willing to be involved in research for human health. Thanks to the University of Tasmania and to Anhui Medical University for providing the scholarship.

To my parents, Ping Tang and Yi Qin, elder sister, Xinlei Peng, brother-in-law, Ziqi Li and fiancé, Guoqi Cai, thanks very much for your unwavering support and love, which encourages me to be better.

Abstract

High blood pressure (BP) is the single greatest risk factor for death from cardiovascular diseases (CVD). High BP is conventionally defined by the systolic BP and diastolic BP, which are the peak and nadir points on the BP waveform, but cannot comprehensively represent systemic arterial haemodynamics. The reservoir-excess pressure model, which was proposed to analyse the BP waveform, provides potentially new information regarding arterial haemodynamics. The reservoir-excess pressure model interprets the BP waveform into a reservoir pressure (RP), which is related to the buffering capacity of elastic arteries, and into an excess pressure (XSP), which is ascribed to wave propagation in the arterial system. Furthermore, reservoir pressure parameters (e.g. RP, XSP and the associated systolic rate constant) have been shown to predict cardiovascular events independent of standard BP and other conventional cardiovascular risk factors. However, non-invasive measurement of reservoir pressure parameters is technically challenging, which limits the widespread application of reservoir pressure parameters. Thus, the overall aims of this research programme were to determine whether reservoir pressure parameters could be non-invasively measured in the human upper arm using an oscillometric cuff device, and further to determine whether cuff device-measured reservoir pressure parameters were clinically relevant – this was assessed by association with cardiovascular risk markers.

In chapter 2, the change in reservoir pressure parameters from the aorta to the brachial and radial arteries was invasively investigated in 51 participants undergoing coronary angiography. A relatively constant RP and an amplified XSP were observed from the aorta to the brachial and radial arteries. These observations provide a new understanding on arterial reservoir pressure parameters and large artery BP physiology.

In chapter 3, the performance of an oscillometric cuff device for measuring the central BP was investigated in 182 people with treated hypertension. The central BP parameters derived from the cuff device were substantially equivalent to the central BP parameters measured using the non-invasive reference standard (radial tonometry) method. This finding is the basis of accurately deriving the reservoir pressure parameters from cuff-based device-measured central BP waveforms.

In chapter 4, whether reservoir pressure parameters could be non-invasively derived from the cuff device-measured brachial or central BP waveform was examined in comparison to true invasive aortic measures among 163 participants undergoing coronary angiography. The brachial-cuff method estimated reservoir pressure parameters had higher concordance with the intra-aortic measures than did the central-cuff method estimated reservoir pressure parameters.

In chapter 5, brachial-cuff reservoir pressure parameters were applied in a large population of Australian adults (n=1874) to examine the potential clinical relevance. Brachial-cuff reservoir pressure parameters were significantly associated with cardiovascular risk markers, indicating their potential clinical significance for predicting cardiovascular risk.

In summary, this thesis determined that reservoir pressure parameters could be reliably estimated on the brachial artery using the non-invasive cuff device, and that these cuff reservoir pressure parameters were related to cardiovascular risk markers. Overall, this research program provides novel information that increases understanding of the reservoir-excess pressure model in humans.

Keywords: arterial blood pressure; blood pressure determination; haemodynamics; reservoir; non-invasive; oscillometry; hypertension; pulse wave analysis; diagnostic equipment

List of Abbreviations

Pressure indices or related terms

BP, blood pressure

RP, reservoir pressure

XSP, excess pressure

Sc, systolic rate constant

Dc, diastolic rate constant

MAP, mean arterial pressure

DBP, diastolic blood pressure

HTN, hypertension

HR, heart rate

AIx, augmentation index

AP, augmentation pressure

PP, pulse pressure

Cardiovascular risk markers

IHD, ischaemic heart disease

T2DM, type 2 diabetes mellitus

cIMT, carotid intima-media thickness

eGFR, estimated glomerular filtration rate

CV events, cardiovascular events

CVD, cardiovascular diseases

LVMI, left ventricular mass index

PWV, pulse wave velocity

Organisations

GBD, Global Burden of Disease

AAMI, Association for the Advancement of Medical Instrumentation

LSAC, Longitudinal Study of Australian Children

ESH, European Society of Hypertension

FDA, Food and Drug Authority

Statistical, measurement or reporting

M, mean

SD, standard deviation

ICC, intra-class correlation coefficient

CI, confidence interval

cm, centimeter

kg, kilogram

mm Hg, millimetre of mercury

n, number of subjects

Miscellaneous

BMI, body mass index

WHR, waist to hip ratio

HDL, high-density lipoprotein cholesterol

P-U, pressure-flow method

FU, follow-up

GTF, generalised transfer function

HF, heart failure

Table of Contents

List of Figures

List of Tables

Preface

High blood pressure (BP) is the number one risk factor for cardiovascular events, and it affects one-fifth of adults.[1, 2] High BP is defined based on the systolic BP and diastolic BP, which are the peak and nadir points on the BP waveform. The BP waveform contains information relating to cardiovascular physiology and pathology, above and beyond simple determination of two numbers (systolic BP and diastolic BP). In recent decades, there are several BP waveform analysis models proposed to interpret BP waveform with BP waveform parameters, which clarities the interaction between the heart and arterial system and provides more detailed information for accurate assessment of cardiovascular diseases. One such concept, the reservoir-excess pressure model, separates the BP waveform into a reservoir pressure, which is related to the buffering capacity of elastic arteries, and an excess pressure, which is ascribed to wave propagation in the arterial system.[3] Moreover, reservoir pressure parameters have been shown to predict cardiovascular events independent of conventional cardiovascular risk factors, including standard BP and Framingham risk score.[4-6]

However, the technical challenge of the non-invasive measurement of reservoir pressure parameters has impeded their widespread use. First, the invasive catheter method for measuring the reservoir pressure parameters cannot be used in daily practice because of the complicated invasive procedure and risk to participants. Second, the principal non-invasive tonometry method for measuring reservoir pressure parameters has not been accepted for clinicians because the operation of the tonometry technique is complicated and requires training. Oscillometric cuff devices are used daily for BP assessment, which is easy-to-handle and operator-independent. One oscillometric cuff (SphygmoCor Xcel, Atcor, Sydney, AU) device has recently been developed to capture BP waveforms, enabling the non-invasive measurement of reservoir pressure parameters. This might facilitate the widespread use of reservoir pressure

parameters, and improve the prediction of cardiovascular events, but has never been investigated. Therefore, the overall aims of this thesis were to determine whether reservoir pressure parameters could be non-invasively measured in the human upper arm using an oscillometric cuff device, and further to determine whether cuff device-measured reservoir pressure parameters were clinically relevant by association with cardiovascular risk markers.

Chapter 1 summarises the current literature related to the reservoir pressure parameters from mechanistic, physiological, technical, and clinical aspects. This provides the background and research gaps relating to reservoir pressure parameters. Chapter 2 determines the changes in reservoir-excess pressure parameters from the aorta to the brachial and radial arteries. This provides greater understanding on the underlying physiology of reservoir pressure parameters in the human large arteries. Chapter 3 determines the ability of an oscillometric brachial cuff device to estimate arterial BP waveform, from which reservoir pressure parameters are consequently derived. This is achieved by comparison of the oscillometric method with standard radial tonometry. Based on the good performance of the cuff device measured arterial BP waveform found in chapter 3, the ability of the cuff device to estimate arterial (both brachial and central) reservoir pressure parameters is further assessed by comparison to the intra-aortic reservoir pressure parameters in chapter 4. Chapter 4 finds better concordance of the cuff device measured brachial reservoir pressure parameters than that of cuff device measured central reservoir pressure parameters to intra-aortic measures. Thus, chapter 5 applies cuff brachial reservoir pressure parameters in a large population of healthy study participants to investigate the association with cardiovascular risk markers. There are significant associations between cuff measured brachial reservoir pressure parameters and cardiovascular risk markers, which indicates the potential clinical utility of cuff measured brachial reservoir pressure parameters. Chapter 6 summarises the future work related to reservoir pressure parameters for improving the assessment of cardiovascular risk.

Chapters 2 to 5 are individually prepared for publication in peer-reviewed scientific journals. Chapters 2, 3 and 4 have been published and chapter 5 is currently being reviewed. For the clarity and consistency of presentation throughout the thesis, slight modifications were made in the writing style and grammar from the published manuscripts, which do not alter the results or conclusions. Additional figures and tables concerning the methods and results of individual studies are added in appendices to help the overall comprehension. The individual studies contribute to the aims of the thesis, and this is specifically outlined at the end of each thesis chapter.

Thesis Aims

Aim 1

To determine the changes in reservoir-excess pressure from the aorta to the brachial and radial arteries.

Hypothesis

Reservoir pressure will be relatively constant, but excess pressure will significantly increase from the aorta to the brachial and radial arteries.

Aim 2

To compare a cuff-based oscillometric device to estimate central BP indices by comparison with radial tonometry measures.

Hypothesis

The cuff-based oscillometric device estimated central BP will be substantially equivalent to central BP estimated using radial tonometry.

Aim 3

To determine whether reservoir pressure parameters can be derived from cuff device-measured brachial or central BP waveforms.

Hypothesis

It will be possible to derive reservoir pressure parameters from cuff device-measured brachial and central BP waveforms.

Aim 4

To determine the associations between brachial-cuff reservoir pressure parameters and cardiovascular risk markers.

Hypothesis

Brachial-cuff reservoir pressure parameters will be significantly associated with cardiovascular risk markers, independent of conventional cardiovascular risk factors.

Chapter 1 – Review of the literature

1.1 Overview:

Cardiovascular disease (CVD) remains a leading cause of death worldwide.[7] High blood pressure (BP) is the number one risk factor for CVD and global disease burden.[8, 9] High BP is defined based on systolic BP and diastolic BP, which are the peak and nadir points on the BP waveform. The reservoir-excess pressure model is a relatively new concept that was proposed in 2003 to derive greater hemodynamic information from analysis of BP waveform.[3] Importantly, recent studies have shown that reservoir pressure parameters predict CVD and cardiovascular events above and beyond conventional cardiovascular risk factors, including the systolic BP and diastolic BP.[4-6, 10-26] This suggests that reservoir pressure parameters may provide additional information to inform CVD risk stratification. However, the technical challenge of their non-invasive measurement has limited the widespread use of reservoir pressure parameters in clinical settings. Greater understanding of the reservoir-excess pressure model from mechanistic, physiological, technical, and clinical aspects will be helpful for determining the potential future clinical role of the measures. The following review summarizes the current literature from these aspects.

1.2 High blood pressure is the number one risk factor for cardiovascular disease

CVD is a class of diseases that involves the heart or blood vessels and is commonly known to include stroke, heart attack, heart failure, and myocardial infarction. Despite improvements in outcomes being achieved, CVD remains the most common cause of death worldwide, with 17.3 million deaths reported in the 2013 Global Burden of Disease (GBD) report.[8, 27] High BP is the major risk factor for CVD, and it affects one-fifth of adults.[1, 2] A meta-analysis with data from more than one million individuals has shown that BP is strongly associated with cardiovascular mortality (e.g., stroke and ischaemic heart disease, as shown in Figure 1.1).[9]

More specifically, each 2 mmHg rise above 115 mmHg in the systolic BP is associated with 7% and 10% increases in mortality risks from ischaemic heart disease and stroke, respectively.[9]

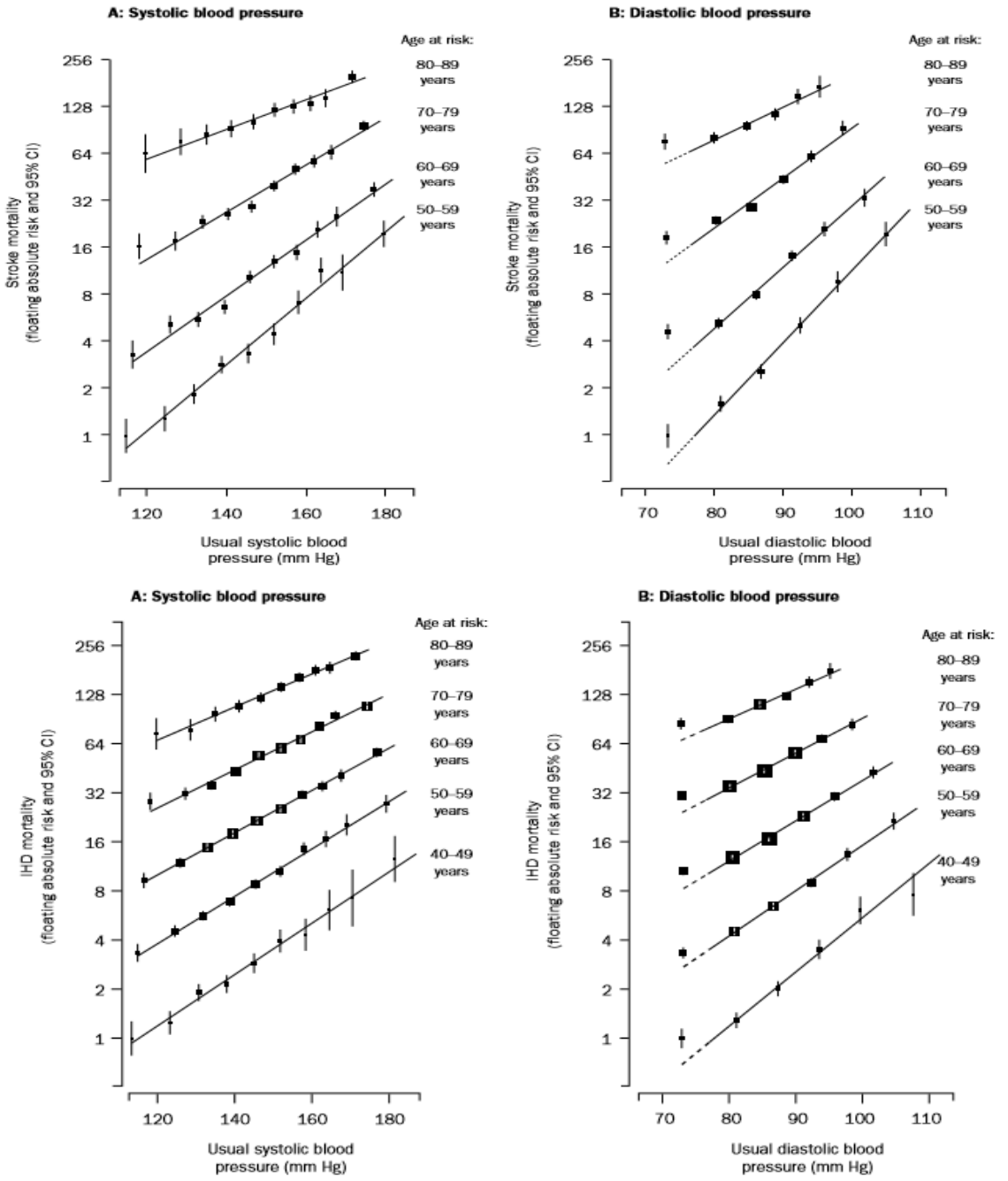


Figure 1.1 Association between systolic (left) and diastolic (right) blood pressures and mortality risks due to stroke (upper) and ischaemic heart disease (IHD, lower). (Figure from Lewington et al., 2002[9])

1.3 How is high BP defined? – Systolic and diastolic BPs

BP is the perpendicular force against the sides of the blood vessels. High BP is defined based on the systolic and diastolic BPs. The systolic BP is the highest pressure in the arterial system and corresponds to the peak cardiac contraction. The diastolic BP is the lowest pressure, which occurs after the end of the relaxation phase of the left ventricule (Figure 1.2). Systolic and diastolic BPs provide "numbers that can be linked in a simplistic way to cardiac strength (systolic BP) and arteriolar tone (diastolic BP)".[28]

The classification of BP varies by region (Table 1.1),[29-31] but lowering of the BP is the unifying goal of intervention and treatment for reducing the incidence of CVD. [32] A recent meta-analysis with 123 studies and 613 815 participants has shown that each 10 mmHg decrease in the systolic BP reduces the risk for major cardiovascular events by 20%, the risk for coronary heart disease by 17%, the risk for stroke by 27%, and the risk for heart failure by 28%, thus leading to a 13% reduction in all-cause mortality.[32]

Table 1.1 Categories of blood pressure in adults.

ESH	SBP		DBP	AHA	SBP		DBP
Optimal	<120	and	<80	NA			
Normal	120- 129	and/or	80-84	Normal	<120	and	80
High normal	130-139	and/or	85-89	Elevated	120-129	and	<80
Grade 1 HTN	140-159	and/or	90-99	Stage 1 HTN	130-139	or	80-89
Grade 2 HTN	160-179	and/or	100-109	Stage 2 HTN	≥140	or	≥90
Grade 3 HTN	≥180	and/or	≥110	NA			
Isolated systolic HTN	≥140	and	<90	NA			

ESH: European Society of Hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; AHA: American Heart Association; HTN: hypertension; NA, not available.

1.4 Limitations of only focusing on the systolic BP and diastolic BP as markers for cardiovascular risk

The arterial pulse consists of numerous continuous values instantaneously determined by left ventricular stroke volume, aortic diameter and stiffness, systemic arterial compliance, peripheral resistance and wave propagation.[33] The arterial pulse is represented by BP waveform, in which systolic BP and diastolic BP refer to the peak and nadir points, respectively (Figure 1.2). Thus, it is obvious that systolic and diastolic BPs cannot comprehensively interpret all the hemodynamic information provided by BP waveform. For example, in Figure 1.3, two individuals with the same systolic BP and diastolic BP (150/80 mmHg) have different BP waveform shapes.[34]

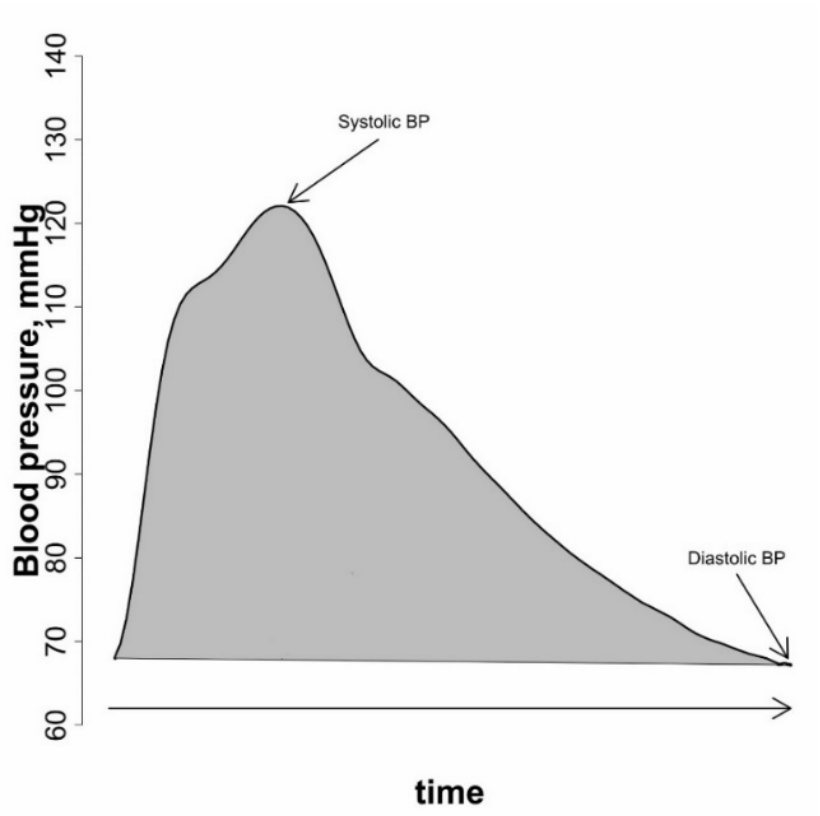


Figure 1.2 Representative blood pressure waveform and illustration of the systolic blood pressure and diastolic blood pressure. BP: blood pressure.

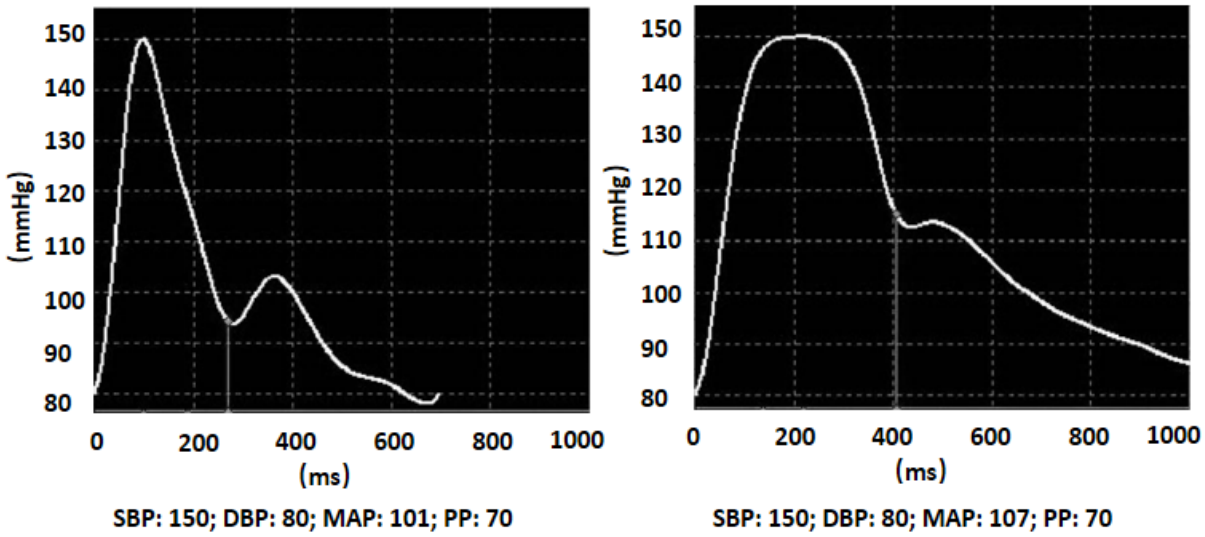


Figure 1.3 Example of two people with the same systolic (SBP) and diastolic (DBP) blood pressures (150/80 mmHg) but different waveform shapes. (Figure from Sharman and Laurent.[34] 2013) Abbreviation: MAP, mean arterial pressure; PP, pulse pressure.

1.5 A potential solution to comprehensively interpret the information of the BP waveform – BP waveform analysis

The intra-arterial BP waveform has become recordable since the first case in patients under anaesthesia seventy years ago.[35] Since then, several BP waveform parameters, such as augmentation pressure and augmentation index, and several BP waveform conceptual models have been proposed to analyse the BP waveform, provides potentially new information regarding arterial haemodynamics. There are two basic conceptual models, the windkessel model and the wave-only model. The windkessel model emphasizes the importance of the arterial compliance in transforming the discontinuous cardiac output into a more steady pressure and flow in diastole, but neglects the wave propagation in the arteries that perfuses the blood volume into peripheral arteries in systole.[36] As a consequence, the windkessel model precisely describes the BP waveform in diastole but fails to explain the sharp upslope of the BP waveform in systole. In contrast, the wave-only model assumes travelling waves are parallel to the artery wall in either forward or backward directions, but does not take into account the waves that are perpendicular to the artery wall – those that are cushioned in systole and discharged in diastole.[37, 38] Thus, the wave-only model plausibly explains the shape of BP waveform but neglects the cushion effect of elastic arteries.[39]

The arterial system has two major functions. First, the arterial system plays a conduit role to deliver blood to the organs and tissues of the body. Second, the arterial system works as a cushion to reduce pulsatile fluctuations generated by the intermittently-pumping left ventricle.[40] When the inflow exceeds the outflow in the arteries, the exceeded wave and energy vertically expand the elastic arteries to buffer the excess inflow.[3] The exceeded wave and energy are stored in the arteries during systole, and released during diastole when there is no blood flowing into arterial system.[3] Both conduit and cushion function play vital roles in blood

propagation and reservation, and thus, should be taken into account to interpret the BP waveform. This requires a more comprehensive conceptual model to explain the BP waveform.

1.6 Reservoir-excess pressure model

The relatively new reservoir-excess model was proposed by J-J Wang[3] in 2003 and was conceived to circumvent conceptual limitations of the windkessel and wave-only models. The reservoir-excess pressure mode interprets the BP waveform as the sum of a RP, determined by the compliance of arterial system, and an XSP, related to local wave propagation.[3] Recent studies have shown that reservoir pressure parameters change in pressure with ageing and exercise,[12,17] and respond to the alterations of cardiac output and wave reflection sites.[41, 42] Furthermore, a number of clinical studies have demonstrated that the prognostic value of reservoir pressure parameters for predicting CVD and cardiovascular mortality is above and beyond conventional cardiovascular risk factors, including standard BP and Framingham risk score.[4-6] However, the issues relating to the measurement location (carotid or radial artery, with or without generalized transfer function involvement) and measurement technique (tonometry or catheter) in some current studies are inconsistent and not clearly clarified.[4, 16, 43] These measurement issues have been briefly raised in a recently published review,[44] but a potential solution was not proposed. The following content of this review will systemically summarize the current literature related to reservoir pressure parameters and make a proposal to address the measurement issues.

1.6.1 What is the reservoir-excess pressure model?

According to the reservoir-excess pressure model, the BP waveform is separated into two components, the RP and XSP (Figure 1.4). The RP represents the reservoir function of the elastic arterial system and is mathematically determined by the difference between the inflow and outflow and arterial compliance (Equation 1.1).[3, 41] Physiologically, the RP increases in

systole to store blood volume when the cardiac input exceeds the output, and decreases in diastole to discharge stored blood volume into peripheral arteries.[41]

$$\frac{d\mathrm{P}_{\mathrm{reservoir}}\,(t)}{dt} = \frac{\mathrm{Q}_{\mathrm{in}}(t) - \mathrm{Q}_{\mathrm{out}}\,(t)}{C}$$

Equation 1.1 Calculation of the reservoir pressure.

The XSP represents the excess work required by the left ventricle for the ejection of stroke volume, and is analogous to flow ejected from the left ventricule.[3] The magnitude of XSP is calculated by subtracting the RP from the total BP, as shown in Equation 1.2.[6]

$$\frac{\mathrm{dP}_{\mathrm{reservoir}}}{\mathrm{dt}} = \mathrm{Sc}(\mathrm{P} - \mathrm{P}_{\mathrm{reservoir}}) - \mathrm{Dc}(\mathrm{P}_{\mathrm{reservoir}} - \mathrm{P}\infty)$$

Equation 1.2 Calculation of the reservoir pressure parameters.

The systolic rate constant and diastolic rate constant of the system are Sc and Dc, respectively, and they represent the rate constants relating to the speeds of the upstroke and downstroke of the BP waveform.[6] Sc=1/ZC (Z is a constant which will depend upon a number of factors, such as the local wave speed and cross-sectional area at the root of the aorta, and C is the compliance of the whole arterial tree), Dc = 1/RC (R is the effective resistance of the peripheral systemic circulation), P is the measured total pressure, $P - P_{reservoir}$ is the excess pressure, and $P\infty$ is the arterial asymptotic pressure. The RP and XSP are expressed in the peak and integral, which are the highest value and the area of the corresponding component respectively.[4, 24] Figure 1.4 is the BP waveform example that is explained by the reservoir-excess pressure model.

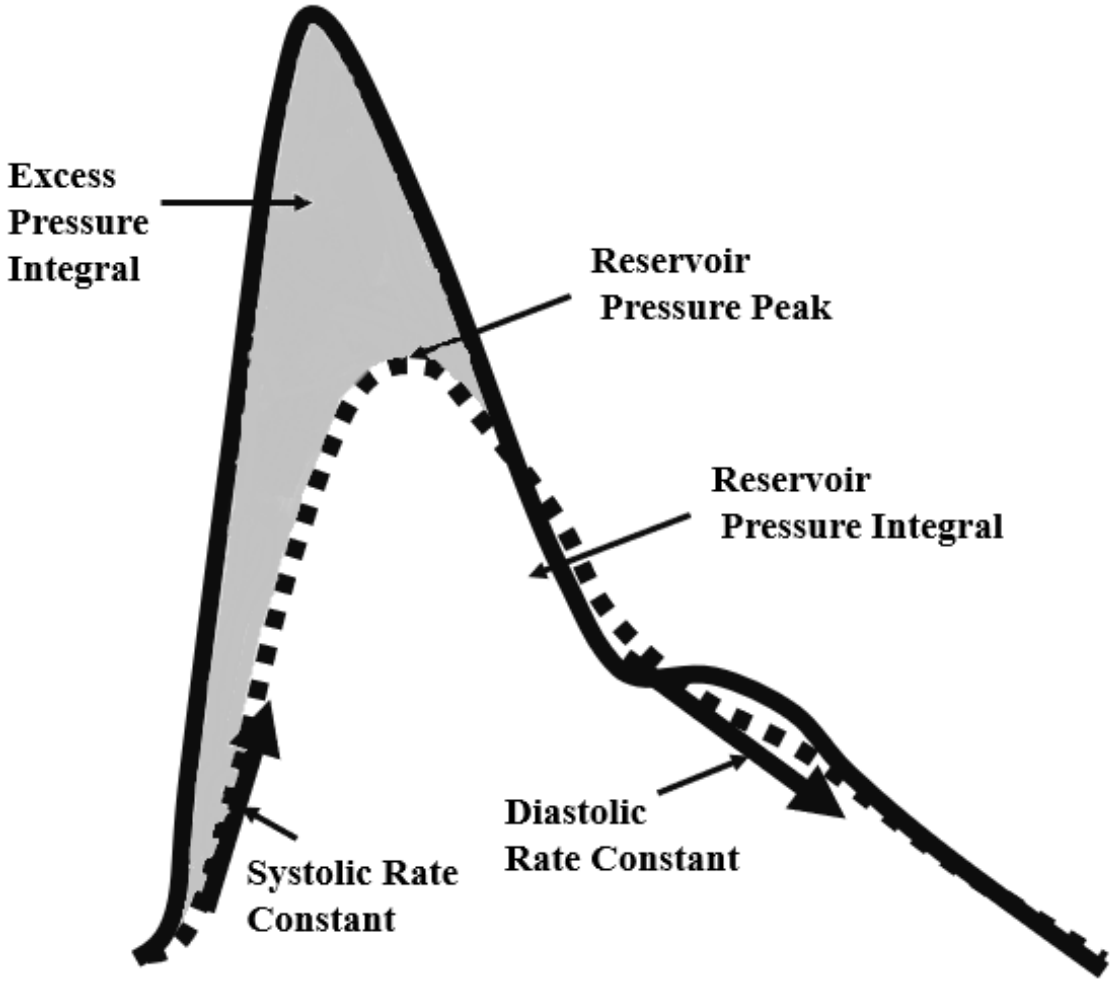


Figure 1.4 Blood pressure waveform (———) with example reservoir pressure parameters. The reservoir pressure (▪▪▪▪▪▪) and excess pressures (in shadow) are expressed as the peak and integral (area under the pressure curves).

1.6.2 Why are the reservoir-excess pressure model and reservoir pressure parameters important?

The reservoir-excess pressure model provides greater hemodynamic information from analysis of BP waveform because it combines the reservoir function of the elastic artery with the wave travelling function of the conduit artery. Ignoring either of these two functions will mislead the explanation of the BP waveform. Without the reservoir function, the BP in diastole will be zero as the aortic valves close, and there is no blood flowing from the heart into the arterial system. On the other hand, neglecting the wave propagation in the conduit arteries will not be able to explain the excess work performed by left ventricular to eject blood into arterial system and result in the inability to explain the BP waveform in systole.

Moreover, the reservoir pressure parameters (e.g., RP peak, RP integral, XSP peak, XSP integral, and Sc) have shown to be clinically relevant to demographic factors (e.g., sex,[14] age,[12,13] heart rate[5, 24] and type 2 diabetes[43]), end-organ damages (e.g., brain structure,[18] aortic stiffness,[21] carotid atherosclerosis[4] and kidney function[19, 23]) and cardiovascular events and mortality[4-6, 20, 22, 24, 26]. The clinical significance of reservoir pressure parameters for predicting cardiovascular events and mortality has been found to be independent of conventional cardiovascular risk factors.[4, 5, 6] Furthermore, the clinical relevance is seemingly applicable to the general population and high-risk population because the subjects in these clinical studies include healthy individuals[6, 13, 14, 16, 18, 21, 23, 24] and individuals with histories of cardiovascular events or clinical symptoms for coronary angiography[4, 6, 10, 17-20, 24-26]. Reservoir pressure parameters also have been shown to effectively respond to anti-hypertension medication,[4] exercise training,[15, 17, 43] and improvement of heart function,[25] demonstrating the potential indicative value of the reservoir pressure parameters for evaluating the effect of CVD. Table

1.2 summarizes the current literature related to the clinical relevance of the reservoir pressure parameters.

Table 1.2 Summary of publications related to the clinical relevance of reservoir pressure parameters.

Study	Subjects	n	Age (M±SD)	Men (%)	Methods					Findings
					Technique	Site	Calibration	GTF	Eq.	
1. Reservoir pressure parameters are related to demographic factors.										
Davies[12], 2010	Undergoing coronary angiography	15	53±10	62	Catheter	Aorta	NA	NA	P-U	- RP increases with ageing
Cymberkno[14], 2011	Healthy	22	20	50	Tonometry	Radial	MAP/DBP	Y	P	- XSP peak and the time to peak XSP are higher in male than in female
Bia[13], 2011	Healthy	43	20-69	35	Tonometry	Radial	MAP/DBP	Y	P	- RP increases with ageing
Hametner[5], 2014	Undergoing coronary angiography	30	64 (55–72)	57	Catheter	Aorta	NA	NA	P	- XSP integral and RP integral increase with ageing - XSP and RP inversely correlate with HR
Davies[4], 2014	Controlled HTN	2069	63±8	81	Tonometry	Radial	Unkwn	N	P	- XSP integral, RP peak, and RP integral inversely correlate with HR
Wang[24], 2017	HF	70	52±16	43	Tonometry	Carotid	MAP/DBP	N	P	- XSP integral is higher in people with HF compared with healthy
Climie[43], 2015	T2DM vs. Non-T2DM	39 vs. 39	62±9 vs. 53±8	49 vs. 51	Tonometry	Radial	Unkwn	N	P	- XSP peak and XSP integral increase, but RP integral decreases during exercise in people both T2MD and non-T2MD - XSP integral inversely correlates with kidney function during exercise in both two groups, and the strength of correlation is stronger in T2DM than in non-T2DM
Schultz[21], 2015	Healthy	359	61±9	49	Tonometry	Radial	SBP/DBP	N	P	- RP integral increases in people with negative stiffness compared to in the people with positive stiffness[#]
2. Reservoir pressure parameters are related to cardiovascular risk markers.										
Sharman[10], 2009	Undergoing dobutamine stress echocardiography	16	62±10	82	Tonometry	Radial	SBP/DBP	N	P	- RP peak positively correlates with AIx

Davies[12], 2010	Undergoing coronary angiography	15	53±10	62	Catheter	Aorta	NA	NA	P-U	- RP integral positively correlates with AIx
Piskorski[16], 2013*	Healthy	159	51±1	45	Tonometry	Radial	Unkwn	Unkwn	P	- XSP integral positively correlates with AP
Climie[18], 2014	T2DM vs. Non-T2DM	37 vs 37	63 ± 9 vs 52±8	47 vs 51	Tonometry	Radial	Unkwn	N	P	- XSP integral inversely correlates with the ratio of grey matter volume to white matter lesions
Davies[4], 2014	Controlled HTN	2069	63±8	81	Tonometry	Radial	Unkwn	N	P	- XSP integral positively correlates with c-IMT
Schultz[21], 2015	Healthy	359	61±9	49	Tonometry	Radial	SBP/DBP	N	P	- RP integral positively correlates with AP, AIx, and LVMI
Climie[23], 2017	Healthy	33	57±9	55	Tonometry	Radial	Unkwn	Unkwn	P	- Change in XSP integral inversely correlates with the change in eGFR
3. Reservoir pressure parameters predict cardiovascular events and mortality.										
Hametner[5], 2014	Undergoing coronary angiography	674	64	57	Tonometry	Radial	SBP/DBP	Y	P	RP integral predicts CV events and mortality (n=128) with 3.8 yrs FU
Davies[4], 2014	Controlled HTN	2069	63±8	81	Tonometry	Radial	Unkwn	N	P	XSP integral predicts CV events (n=134) with 3.4 yrs FU
Narayan[20], 2015	Elderly HTN	838	65 to 84	46	Tonometry	Carotid	MAP/DBP	N	P	Sc predicts CV events (n=81) with 4.4 yrs FU
Cheng[6], 2016	Normotensive and untreated hypertensive of history of CVD	1272	52±13	54	Tonometry	Carotid	MAP/DBP	N	P	RP peak, RP integral, Sc, and Dc predict CV mortality (n=315) with 19.8 yrs FU
	Healthy without a history of CVD	2221	53±12	46	Tonometry	Radial	SBP/DBP	Y	P	Sc and Dc predict CV mortality (n=171) with 10 yrs FU
Parragh,[22] 2016*	HF undergoing coronary angiograph	83	61	89	Tonometry	Radial	Unkwn	Y	P	RP peak <16.6±2.8 mmHg and >26.1±3.2 mmHg predicts CV events (n=30) with 3.5 yrs FU
Wang[24], 2017	Healthy control	70	63±18	47	Tonometry	Carotid	MAP/DBP	N	P	XSP integral predicts total mortality (n=56) with 9.9 yrs FU
Schneider,[26] 2018	People with acute coronary syndrome and diminished ejection fraction	251	64	71	Tonometry	Radial	Unkwn	Unkwn	P	XSP integral predicts CV events (n=78) with 3.4 yrs FU
4. Reservoir pressure parameters response to intervention.										

Sharman[10], 2009	Undergoing dobutamine stress echocardiography	16	62±10	82	Tonometry	Radial	SBP/DBP	N	P	- RP peak decreases, and XSP peak increases after stress induced by dobutamine
Schultz[17], 2013	Clinically referred to coronary angiography	10	55±10	70	Catheter	Aorta	NA	NA	P	- RP integral decreases, and XSP increases during exercise
Heffernan[15], 2013	Pre-HTN or untreated HTN	21	61±1	27	Tonometry	Radial	Unkwn	N	P	- RP peak decreases after 12 weeks of resistance exercise training
Davies[4], 2014	Controlled HTN	2069	63±8	81	Tonometry	Radial	Unkwn	N	P	- XSP integral and RP integral are lower in the patients with medication of amlodipine + perindopril compared with those with atenolol + bendroflumethiazide
Climie[43], 2015	T2DM	37	63 ± 9	47	Tonometry	Radial	Unkwn	N	P	- XSP integral increases after exercise
Wohlfahrt[25], 2017	HF	38	73±7	53	Tonometry	Radial	Unkwn	Y	P	- RP peak increases after the improvement of heart function

RP or XSP expressed alone without peak or integral is due to that it is not specified in the corresponding literature. M±SD: mean ± standard deviation. In the calibration column, MAP/DBP indicates that the peripheral blood waveform is calibrated with the mean arterial pressure and diastolic blood pressure; SBP/DBP indicates that the peripheral blood waveform is calibrated with the systolic blood pressure and diastolic blood pressure; NA indicates that the central BP waveform does not need to undergo the calibration process because the waveform is invasively captured; and unkwn indicates that the information of the calibration is not clearly clarified. GTF: generalized transfer function. In the GTF column, Y indicates that GTF is applied; N indicates that GTF is not applied; N/A indicates that the catheter measurement does not need to apply to GTF; and unkwn indicates that the use of GTF is not clearly clarified. Eq: equation. In the equation column, P refers to the pressure-only method and P-U refers to the pressure-flow method for deriving the reservoir pressure parameters. yrs: years; RP: reservoir pressure; XSP: excess pressure; Sc: systolic rate constant; Dc: diastolic rate constant; HTN: hypertension; HR: heart rate; LVMI: left ventricular mass index; c-IMT: carotid intima-media thickness; AP: augmentation pressure; T2DM: type 2 diabetes mellitus; CV: cardiovascular; CVD: cardiovascular diseases; HF: heart failure; eGFR: estimated glomerular filtration rate; *: abstract in artery research;#, negative stiffness refers to brachial PWV<aortic PWV, and positive stiffness refers to brachial PWV>aortic PWV; n in the findings column refers to the incidence of cardiovascular events and mortality,

1.6.3 Physiological basis of the reservoir-excess pressure model

RP is theorized to increase in systole to store blood volume and decrease in diastole to discharge blood volume, which is proposed based on the extremely concordant shape among the volume change, difference in the inflows and outflows, and calculated RP in the canine thoracic aorta (Figure 1.5).[3] Physiologically, when the heart contracts in systole, a large amount of blood (approximately 40% of the stroke volume) ejected from the heart is reserved in the aorta to mitigate the cyclic pulsatile fluctuation in BP.[3] This ensures the outflow in diastole to maintain the level of BP and supplies continuous blood into the peripheral vasculature and vital organs. When the heart relaxes and the aortic valve closes in diastole, there is no blood flowing into the aorta, and RP declines to recoil the stored blood volume and energy into the distal vasculature. The arterial reservoir function has been further confirmed in humans by Schultz and colleagues[41], who found that the RP corresponds to blood volume changes in the ascending aorta. On the other hand, XSP is theorized as the excess work required by the left ventricle for the ejection of stroke volume, and is analogous to aortic inflow. Indeed, after subtracting the RP from total BP, the XSP is proportional to the aortic inflow (Qin) with a strong correlation (XSP=0.38×Qin+0.0951).[3]

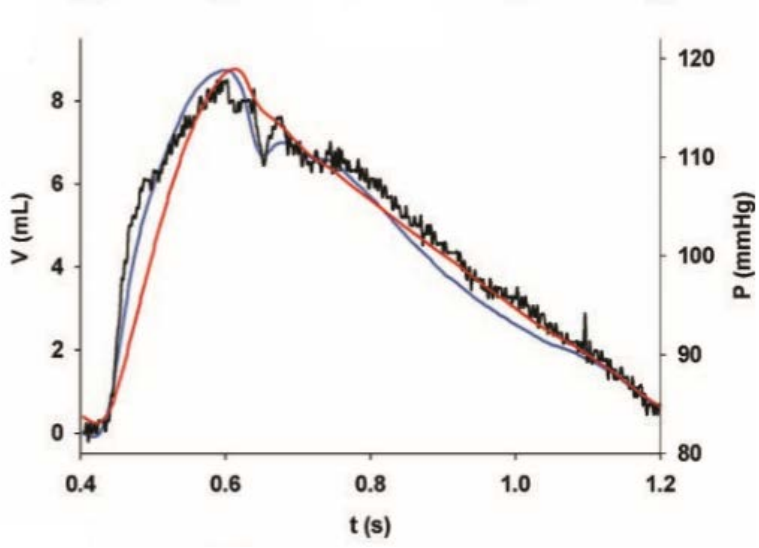


Figure 1.5 Magnitude of the volume change in the thoracic aorta calculated by ultrasound measurements (black line) and by differences of inflows and outflows (blue line) plotted with the calculated reservoir pressure (red line). (Figure from Wang et al., 2003[3])

In general, the shape of the BP waveform becomes steeper at the distal arteries compared with at the proximal arteries due to the tapering arterial diameter and increased arterial resistance in the periperhery, and this is termed BP amplification (Figure 1.6).[45-47] The RP and XSP are the two components of the total BP waveform, and thus are supposed to be altered to some extent with the BP amplification. Indeed, studies have shown that the RP is relatively constant whereas the XSP is amplified from the canine ascending aorta to the aortic arch, thoracic aorta and abdominal aorta, as shown in Figure 1.8.[3, 48-51] Moreover, the modification of the XSP is seemingly analogous to the systolic BP amplification (Figure 1.7).[47] A similar finding has been reported from an invasive study in humans in which the RP is relatively constant and the XSP is increased from the ascending aorta to the arch and diaphragm and renal and bifurcation arteries (25.3, 26.5, 31.8, 36.1, and 39.4 mmHg, respectively).[49] All of the current studies related to the amplifcation of reservoir pressure parameters are conducted in the aortic trunk. However, application of reservoir pressure parameters in clinical settings requires their non-invasive measurement at the peripheral arteries, commonly performed at the brachial and radial arteries. Therefore, physiological studies related to the reservoir pressure parameters in the human upper arm are needed. *Chapter 2 of this thesis aimed to determine the changes in the reservoir pressure parameters from the aorta to the brachial and radial arteries in 51 participants undergoing diagnostic coronary angiography.*

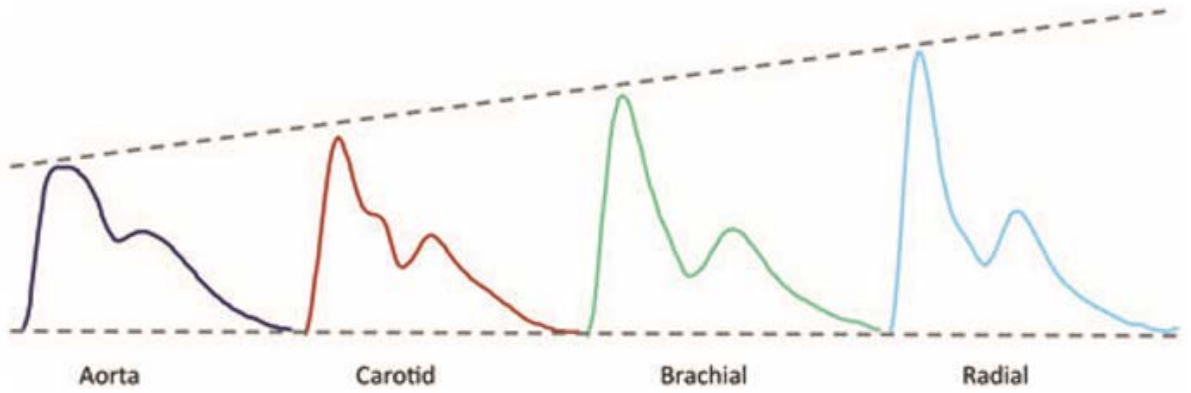


Figure 1.6 Amplification of the blood pressure waveform moving from the aorta to the carotid, brachial and radial arteries.(Figure from Lewington et al., 2002[47])

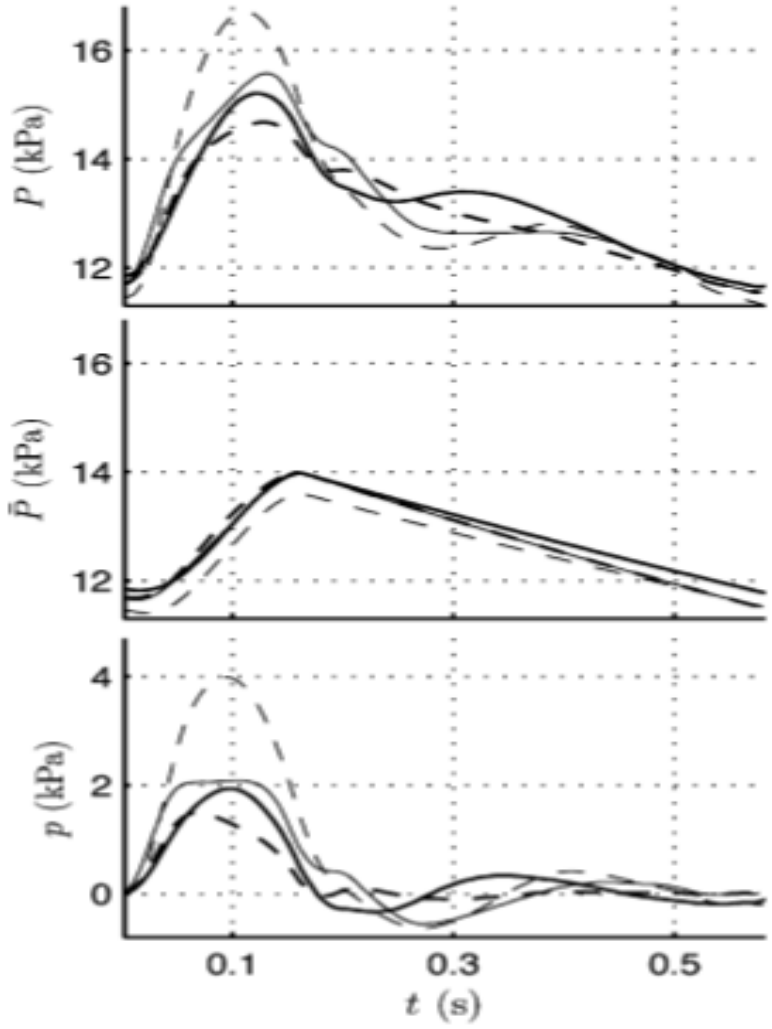


Figure 1.7 Pressure (P) recordings at the ascending aorta, aortic arch, thoracic aorta and abdominal aorta in a dog, and their corresponding reservoir pressure and excess pressure. (*P*: total blood pressure; $\bar{P}$: reservoir blood pressure; *p*: excess blood pressure; thick solid curves: ascending aorta; thick dashed curves: aortic arch; thin solid lines curves: thoracic aorta; thin dashed curves: abdominal aorta). (Figure from Aguado-Sierra et al., 2008[48])

1.6.4 Measurement of the reservoir pressure parameters

The reservoir pressure parameters are initially measured with the catheter system from inside the aorta, and this is the reference standard measurement method. Tonometry is presently the principal non-invasive method to measure reservoir pressure parameters. However, neither catheter nor tonometry methods have been used in clinical practice for reservoir pressure parameters measurement because of the complicated procedure and training requirement. Thus, a non-invasive and easy-to-operate method to measure reservoir pressure parameters is required. Recent technology advancement allows measuring of BP waveforms using standard oscillometric cuff method, which is routinely used for BP assessment. These cuff BP waveforms can theoretically be used for deriving reservoir pressure parameters, but this has never been determined. The next content will elaborate the current circumstance of the catheter and tonometry method and propose the potential application of cuff method on the measurement of the reservoir pressure parameters.

1.6.4.1 Invasive catheter method

The invasive catheter technique is the gold standard method of reservoir pressure measurement. This technique is only performed for cardiovascular investigation in a hospital setting. According to the standard clinical procedure, a catheter (solid-state or fluid-filled catheter) is inserted into radial or femoral artery, via a puncture, to reach the ascending aorta. Aortic BP waveforms are recorded by an analogue-to-digital signal converter (Lab view, AD Instruments, Bella Vista, Australia) within LabChart software (AD Instruments, Bella Vista, Australia). Reservoir pressure parameters are derived from the catheter measured intra-aortic BP waveforms. The reservoir pressure parameters at the ascending aorta are recognized as the most crucial among arterial system because the arterial hemodynamics at ascending aorta presents

the pressure load experienced by the organs, especially the heart, but is also relevant to the health of the brain, kidneys and eyes.

A strength of the catheter method is that it can avoid the influence of artefact introduced from non-invasive techniques, and it provides the most accurate reservoir pressure parameters. The catheter method has been used to assess the validity of tonometry-measured reservoir pressure parameters,[5] the change of reservoir pressure parameters with aging and exercise[17, 50] and the clinical significance of reservoir pressure parameters[5, 12]. However, the invasive clinical procedure requires skilled clinicians and high costs, and introduces risk to participants, and thus cannot be performed in daily practice on the wider population.

1.6.4.2 Non-invasive tonometry method

The tonometry technique is the principal non-invasive method that has been applied in the measurement of reservoir pressure parameters. Applanation tonometry was developed for measuring the BP waveform.[52] The technique uses a strain gauge pressure transducer (Millar Instruments Inc., Houston, TX) mounted on the tip of a probe that can be handheld. The transducer is coplanar with a large area of flat surface where in contact with the skin overlying the strongest pulse above the carotid and radial arteries to obtain BP waveforms.[53] The tonometry-measured radial BP waveform can be used to generate a central BP waveform via a peripheral-to-central generalized transfer function (GTF). Altogether, tonometry methods can measure carotid and radial BP waveforms and estimate central BP waveforms, which enables the estimation of carotid, radial and central reservoir pressure parameters. Carotid reservoir pressure parameters are recognized as a surrogate for central reservoir pressure parameters on the basis of the substantial equivalence between central and aortic BP.[20]

Tonometry measured carotid, radial and central reservoir pressure parameters have been shown to predict CVD and CV events independent of conventional cardiovascular risk factors.[4, 20, 22,

[25] However, the tonometer probe needs to be held perpendicularly to the artery with a gentle hold-on pressure for obtaining consistent BP waveforms, which requires training for operators. This is one factor that impedes acceptance of tonometry by clinicians and the method has not been widely used. Therefore, a more operator-independent method is required to measure reservoir pressure parameters in clinical settings.

1.6.4.3 Non-invasive cuff method

Oscillometric cuff measurement of BP is the most common method to record standard BP in clinical practice. One such device (Sphygmocor Xcel, Atcor, Sydney, AU) has been developed to measure the brachial oscillometric waveform and estimate the central BP waveform via a GTF.[54, 55] Operation of the SphygmoCor device involves four steps: 1) conventional brachial BP measurement; 2) brachial oscillometric waveform acquisition; 3) brachial BP waveform calibration, usually with cuff systolic BP and diastolic BP (although mean arterial pressure and diastolic BP can be applied); 4) central BP waveform estimation via a GTF. Figure 1.8 outlines the process of BP waveform measurement using the SphygmoCor Xcel. Both the cuff measured brachial BP waveform and the estimated central BP waveform can theoretically be used to derive reservoir pressure parameters.

All these procedures above are automatic after pressing the "start" button, which is more clinically practical and operator-independent than the catheter and tonometry methods. However, the validity of cuff-measured central BP waveform has not been assessed in a large population, which is the basis to derive cuff-central reservoir pressure parameters. Although there is one study that has determined the performance of the cuff device on estimation of central BP in 30 healthy subjects,[56] a minimal sample size of 85 people is required to assess the validity of non-invasive BP measurement devices according to the Association for the Advancement of Medical Instrumentation (AAMI) standard.[57] *Therefore, chapter 3 of this*

thesis determined the estimate of central BP using the cuff device in a large well-characterized population (n=182). This was achieved by comparison of the cuff-measured central BP parameters to the non-invasive reference standard.

The need of an "easy-to-handle and operator-independent" device for measuring reservoir pressure parameters has been raised in a recently published review,[44] and this can seemingly be achieved with the cuff technique. However, whether reservoir pressure parameters could be derived non-invasively from the cuff measured brachial BP waveforms or central BP waveforms has never been investigated. *Therefore, chapter 4 of this thesis assessed concordance of cuff-measured reservoir pressure parameters with the simultaneously measured invasive aortic reservoir pressure parameters in 162 participants. If reasonable concordance between cuff-measured and the gold standard intra-aortic reservoir pressure parameters was found in chapter 4, chapter 5 would determine the clinical relevance of cuff-measured reservoir pressure parameters. This will be determined by association with cardiovascular risk markers (carotid atherosclerosis and large arterial stiffness) in a large population of Australian adults.*

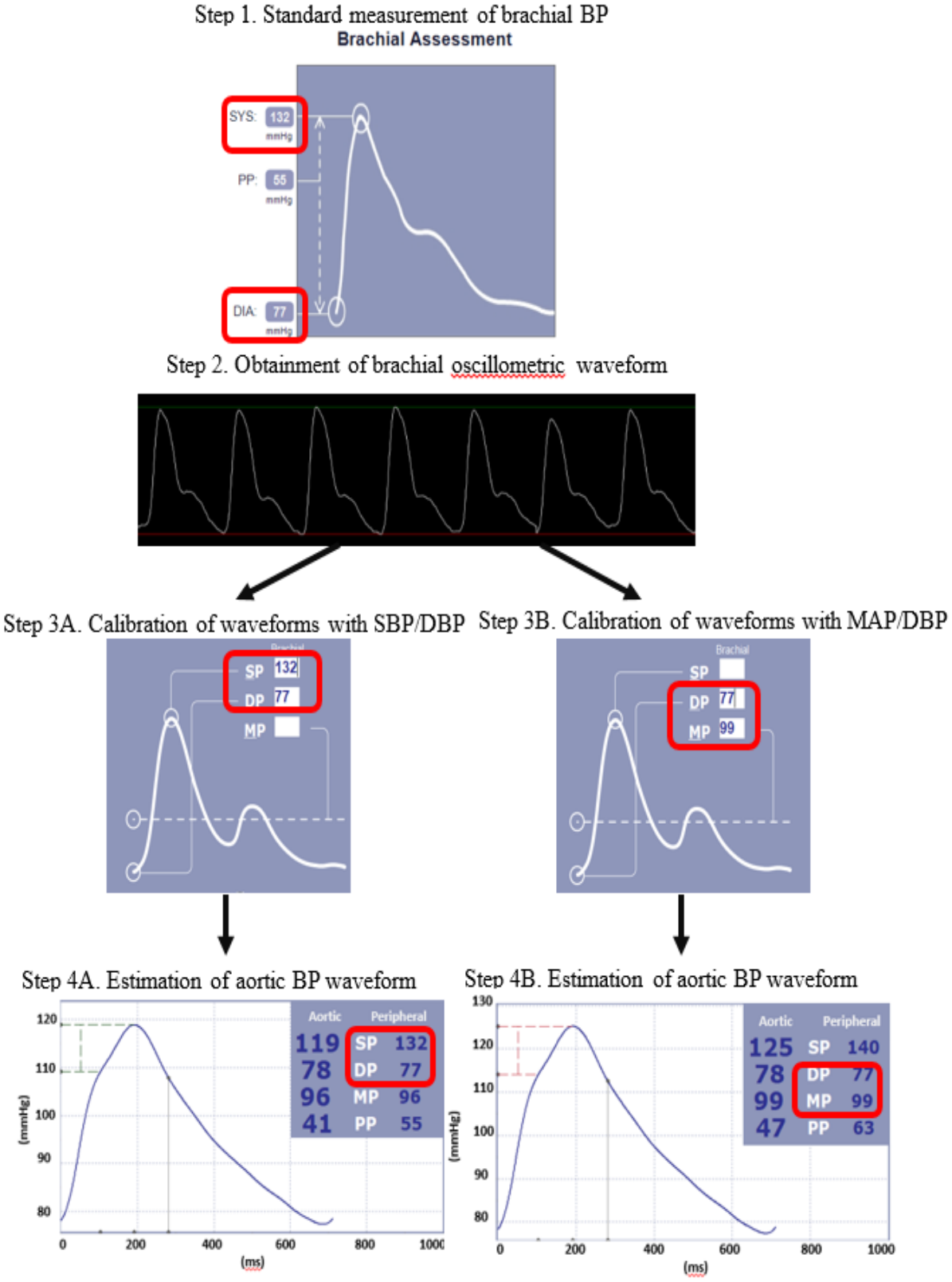


Figure 1.8 Process of the BP waveform measurement using the SphygmoCor Xcel. SBP and SP refer to the systolic blood pressure; DBP and DP refer to the diastolic blood pressure; MAP and MP refer to the mean arterial pressure calculated using the equation 0.4×(SBP-DBP) +DBP in this example. See the figure text for details.

1.7 Summary

This review of the literature highlights the importance of reservoir-excess pressure model. In general, reservoir pressure parameters may provide more detailed information of systemic arterial hemodynamics than do conventional systolic BP and diastolic BP. Furthermore, reservoir pressure parameters are related to demographic factors, cardiovascular risk markers, and cardiovascular events above and beyond conventional cardiovascular risk factors. However, widespread application of reservoir pressure parameters has been impeded by the technical challenge of the clinically non-invasive measurement. A potential solution to address the technical challenge is proposed based on the pioneering SphygmoCor Xcel cuff derived reservoir pressure parameters. Further studies should be directed towards testing the validity of reservoir pressure parameters measured using the cuff technique and their potential clinical significance, as the cuff measured reservoir pressure parameters may improve cardiovascular risk stratification.

Chapter 2 – Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper-arm

This thesis chapter has been published and formatted according to *Journal of Hypertension.*

Peng X, Schultz MG, Picone DS, Black JA, Dwyer N, Roberts-Thomson P, Davies JE, and Sharman JE. Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper-arm. *Journal of Hypertension*. 2017 Sep; 35(9):1825-1831.

Link to online article: https://www.ncbi.nlm.nih.gov/pubmed/28505065

doi: 10.1097/HJH.0000000000001400.

Citations: 3

Presentations:

- Arterial Hemodynamics Oral Presentation, London, UK, June 2016 (supervisor presented it on my behalf)
- International Society of Hypertension poster presentation, Seoul, South Korea, September 2016

2.1 Abstract

Background. Arterial reservoir characteristics are related to blood pressure (BP) and independently predict cardiovascular events. It is unknown if arterial reservoir characteristics are modified from the central-to-peripheral large arteries, and whether there is a contributory role to BP amplification. The aim of this study was to assess central-to-peripheral changes in arterial reservoir characteristics and determine associations with BP. **Methods.** Reservoir pressure (RP), excess pressure (XSP) were derived from intra-arterial BP waveforms among 51 participants (aged 63 ±13 years, 63% male) undergoing clinically indicated cardiac angiography. BP waveforms were recorded in the ascending aorta, brachial (mid-humerus) and radial (wrist) arteries via catheter pull-back. **Results.** There was no significant difference in RP between arterial site (54 ±15; 53±15; and 52±17 mmHg, p=0.68 for RP peak and 2799.1±818.5 $Pa{\cdot}s^{-1}$; 2657.8±775.1 $Pa{\cdot}s^{-1}$; and 2499.5±764.5 $Pa{\cdot}s^{-1}$, p=0.16 for RP integral from the aorta to brachial and radial artery, respectively). Conversely, XSP increased stepwise from the aorta to the brachial and radial arteries (24±11; 42±14; 53±16 mmHg for XSP peak, and 538.3±302.8 $Pa{\cdot}s^{-1}$; 788.4±369.7 $Pa{\cdot}s^{-1}$; and 875.1±434.7 $Pa{\cdot}s^{-1}$ for XSP integral, both p<0.001), as did systolic BP (134±18; 141±16; 146 ±19 mmHg, p=0.004). There were highly significant associations between RP and systolic BP at all arterial sites (r=0.821; 0.649; 0.708, p<0.001 for all), but the strength of associations between peak XSP and systolic BP increased significantly from the aorta to the radial artery (r=0.121; 0.508; z=3.04, p=0.004). **Conclusion.** Arterial reservoir pressure and excess pressure are modified through the large arteries of the upper-limb. Whilst RP remains relatively constant, XSP increases significantly and is highly related to BP (SBP and PP) amplification. These data provide a new understanding on arterial reservoir characteristics and large artery BP physiology.

2.2 Introduction

Central blood pressure (BP) parameters (systolic blood pressure [SBP] and pulse pressure [PP]) predict future cardiovascular events.[47, 58] These pulsatile components of the pressure waveform become amplified as the arterial pressure pulse propagates from the heart and large elastic aorta towards the relatively smaller and more muscular arteries (brachial and radial) in the periphery.[46] Thus, in most people, the peripheral SBP and PP are higher than in the aorta, although there is significant individual variability.[59, 60] The cause of these central-to-peripheral changes is not fully understood but is thought to be due to differences in arterial structure that affect local haemodynamics, including a progressive reduction of vessel diameter, together with an increase in relative wall thickness and stiffness towards the periphery.[46]

BP amplification within the large arteries is commonly interpreted by a 'wave only' model of arterial physiology.[61] An alternative idea (the reservoir-excess pressure concept) views BP as a composite of an arterial 'reservoir' (dependant on global arterial compliance and resistance) in addition to an 'excess' (wave-related) component.[62] Parameters derived from this model (e.g. reservoir pressure, RP; excess pressure, XSP; systolic and diastolic rate constants) predict cardiovascular events and markers of target organ damage independent of brachial BP and other cardiovascular risk factors, including Framingham risk score.[4-6] Whether RP and XSP change as SBP and PP amplify from the aorta to the arm where BP is traditionally measured has never been investigated, but may help to explain the mechanisms of BP amplification. The aim of this study was to determine if RP and XSP change in magnitude from the aorta to the brachial and radial arteries, and, if so, to determine whether these changes are associated with amplification in SBP and PP. On the basis of previous data within the human aorta,[63] we hypothesized that RP would remain relatively uniform from central-to-peripheral arteries but XSP would increase peripherally and correlate with SBP and PP amplification.

2.3 Methods

Participants. Patients scheduled for diagnostic coronary angiography at the Royal Hobart Hospital (Hobart, Australia) provided written consent to participate in this study. Exclusion criteria were: an inter-arm SBP difference >5 mmHg (based on pre-angiogram simultaneous brachial cuff BP measures in duplicate);[64] medical or procedural issues that arose during the angiogram that precluded the research measures; poor-quality waveforms due to technical difficulties during data acquisition, participants with atrial fibrillation or aortic stenosis; and technicalities related to waveform analysis (as described below). The full study protocol was completed in 51 participants (Supplementary figure 1). The study was approved by University of Tasmania Human Research ethics committee. All research procedures were carried out in accordance with the Declaration of Helsinki.

Data acquisition. All participants were studied under stable haemodynamic conditions, clear of medications that could have acutely affected BP. Arterial pressure waveforms were acquired via a fluid-filled catheter inserted at the radial artery after completion of the clinical procedure. The types of catheter used for pressure measurements included 5-6F Judkins Left (Cordis, NJ), multipurpose (Cordis), and TIG (Terumo, NJ). In each participant, the catheter was placed in the ascending aorta approximately 1-5 cm above the aortic valve to record aortic pressure waveforms. The catheter was then sequentially pulled back into the upper arm (mid-humerus) for brachial waveform measurement, and then to the wrist (as distal as possible by slightly withdrawing the sheath radially) for radial waveform measurement. The catheter position at each arterial location was confirmed by fluoroscopy, and the catheter was flushed before waveform acquisition began. Due to the time restriction for catheterisation procedure, only one measurement was obtained at each arterial location. Stable pressure waveforms were recorded for a minimum of 20 seconds at each arterial location (incorporating a number of respiratory

cycles) via analogue-to-digital signal converter (Lab view and LabChart 7 software AD Instruments, Bella Vista, Australia) at a frequency of 1000 Hz. The total time taken to complete all measures was approximately three minutes. The dynamic response of the fluid-filled catheter system was assessed by performing 'pop-tests' and confirmed in the appropriate range outlined by Gardner et al.[65] (natural frequency >18 Hz and the damping coefficient >0.3). Participant clinical characteristics were extracted from medical records.

RP, XSP, and other hemodynamic parameters. Raw pressure waveform signals were calibrated offline using 2-point calibration method to convert units of measurement from Volts to mmHg as previously described.[66] Waveforms were then ensemble averaged to derive reservoir parameters. RP was calculated according to the methods outlined by Davies et al.[4] in a customized Matlab program, based on equation 2.1 using pressure-only.[39] The systolic and diastolic rate constants (i.e. the time constants relating to the speed of upstroke and downstroke of the pressure waveform respectively) of the system are Sc and Dc, where a = 1/ ZC and b = 1/RC (Z is a constant which will depend upon a number of factors, such as the local wave speed and cross-sectional area at the root of the aorta, and C is the compliance of the whole arterial tree, and R is the effective resistance of the peripheral systemic circulation).[16] P is measured total pressure and P_∞ is the arterial asymptotic pressure. XSP was calculated by subtracting RP from the total pressure. Whilst the RP algorithm accommodates waveforms with exponential pressure decay during diastole, those with apparent 'linear' fall during diastole can generate negative waveform parameter values, which are physiologically implausible. Fifteen aortic, five brachial and six radial measurements were excluded for this reason (Appendix figure 1.1).

$$\frac{dP_{reservoir}}{dt} = Sc(P - P_{reservoir}) - Dc(P_{reservoir} - P\infty)$$

Equation 2.1 Calculation of the reservoir pressure.

The percentage contribution of RP to total pressure (proportion RP) was calculated as RP integral / total pressure integral×100. The percentage contribution of XSP to total pressure (proportion XSP) was defined 100% - proportion RP. The ratio of XSP contribution to RP contribution in the total pressure (XSP:RP ratio) was calculated as the proportion XSP/ proportion RP. PP was defined as SBP-DBP. Augmentation pressure (AP) was calculated as the difference between the second and the first systolic peaks (P2-P1). Augmentation index (AIx) was defined as the percentage ratio of AP/ PP when P1<P2, and the percentage ratio of P2/P1 when P1≥P2.[67]

Statistical analysis. All statistical analysis was performed in SPSS for Windows software (version 22.0; SPSS Inc., Chicago, IL). Differences in hemodynamic parameters between each arterial region were assessed by one-way analysis of variance. Associations between waveform indices (SBP and PP) and RP and XSP were assessed by Pearson correlation, and Z scores were calculated to compare the regression slopes. $P<0.05$ was considered statistically significant.

2.4 Results

Clinical characteristics. The study population characteristics are summarised in Table 2.1. Participants were predominantly male and middle-to-older age. On average, kidney function was slightly impaired according to estimated glomerular filtration rate. The prevalence of hypertension (physician diagnosis) was high (88%), and calcium channel blockers were the most commonly used class of antihypertensive medication. A third of participants had diabetes mellitus and most participants had non-significant, or single-vessel, coronary artery stenosis.

Table 2.1 Clinical characteristics of participants.

Variable	Mean (SD) or n (%)
Age (years)	62.6 (13.0)
Sex (men %)	36 (63)
Body mass index ($kg \cdot m^{-2}$)	25.0 (9.3)
Hypertension	45 (88)
Estimated glomerular filtration rate ($mls/min/1.73m^2$)	79.3 (20.0)
Diabetes	14 (30)
Smoker	25 (38)
Angiographic findings	
Non-significant disease	20 (40)
Single vessel	19 (38)
Double vessel	7 (14)
Multi-vessel	4 (8)
Lipid profile $mmol \cdot L^{-1}$	
High-density lipoprotein cholesterol	1.4 (0.5)
Low-density lipoprotein cholesterol	2.6 (1.0)
Triglycerides	1.9 (1.2)
Drug therapy	
Diuretic	2 (5)
Beta blocker	7 (17)
Calcium channel blocker	34 (81)
Angiotensin converting enzyme inhibitor	3 (7)
Statin	3 (7)

Haemodynamics from the aorta to the brachial and radial arteries. SBP and PP were significantly raised at the radial artery compared to the aorta, whilst DBP remained relatively constant (on average) from the aorta to the brachial and radial arteries. RP was not significantly different between any of the arterial sites, whether expressed as the peak or integral component. However, XSP integral was significantly increased at the brachial and radial arteries compared to the aorta, as was XSP peak (Table 2.2). The systolic rate constant decreased significantly from the aorta to the brachial and radial arteries, and the diastolic rate constant was decreased at the radial artery compared to the aorta (Table 2.2). Proportion RP was highest in the aorta compared to the brachial and radial arteries. Conversely, proportion XSP was significantly higher at the brachial and radial arteries compared to the aorta. XSP:RP ratio was significantly increased from the aorta to the radial artery, indicating a greater proportion of radial pressure attributable to XSP compared to the aorta (Table 2.2). AP was positive at the aorta, and significantly decreased to be negative at the brachial and radial arteries. AIx was increased stepwise from the aorta to the brachial and radial artery. Central-to-peripheral changes in RP and XSP parameters were not associated with age (see appendix table 1.1), nor associated with smoking status, diabetes, hypertension, number of vessels stenosed or estimated glomerular filtration rate. To illustrate central-to-peripheral differences in pressure waveforms, a representative example from one of the participants is presented in Figure 2.1.

Table 2.2 Comparison of invasive arterial RP and XSP and blood pressure parameters along the arteries.

Variable	Site			p-value
	Aorta	Brachial artery	Radial artery	
SBP (mmHg)	134.0 (17.8)	141.0 (16.3)	145.9 (19.0)*	0.004
DBP (mmHg)	65.6 (8.7)	63.1 (8.3)	61.0 (8.2)*	0.025
PP (mmHg)	68.4 (16.4)	77.8 (14.3)*	84.9 (19.3)*	<0.001
RP integral ($Pa \cdot s^{-1}$)	2799.1 (818.5)	2657.8 (775.1)	2499.5 (764.5)	0.16
RP peak (mmHg)	54.2 (15.4)	52.8 (14.8)	51.5 (17.0)	0.68
XSP integral ($Pa \cdot s^{-1}$)	538.3 (302.8)	788.4 (369.7)*	875.1 (434.7)*	<0.001
XSP peak (mmHg)	23.7 (10.5)	41.6 (14.1)*	52.6 (15.6)*ǂ	<0.001
Proportion RP (%)	83.4 (9.4)	76.7 (10.6)*	73.7 (11.9)*	<0.001
Proportion XSP (%)	16.6 (9.4)	23.3 (10.6)*	26.3 (11.9)*	<0.001
XSP:RP (ratio)	0.27 (0.23)	0.33 (0.20)	0.40 (0.27)*	0.020
Pinf (mmHg)	57.3 (10.9)	53 (10.0)	51.4 (8.9)*	0.009
Systolic rate constant (s^{-1})	0.1883 (0.0839)	0.1318 (0.0905)*	0.1108 (0.0808)*ǂ	<0.001
Diastolic rate constant (s^{-1})	0.0254 (0.009)	0.0222(0.0088)	0.0210(0.084)*	0.035
AP (mmHg)	16.8 (16.5)	-3.4 (18.9)*	-21.5 (19.8)*ǂ	<0.001
AIx (%)	38.9 (28.5)	57.0 (38.0)*	77.5 (26.1)*ǂ	<0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; RP: reservoir pressure; XSP: excess pressure; Proportion RP: the percentage contribution of RP to total pressure; Proportion XSP: the percentage contribution of XSP to total pressure; XSP:RP: the ratio of XSP contribution to RP contribution in the total pressure; Pinf, pressure level; AP: augmentation pressure; AIx: augmentation index; P1: the first systolic peak; P2; the second systolic peak, data are mean (SD), * $p<0.05$ vs. aorta; ǂ $p<0.05$ vs. brachial artery.

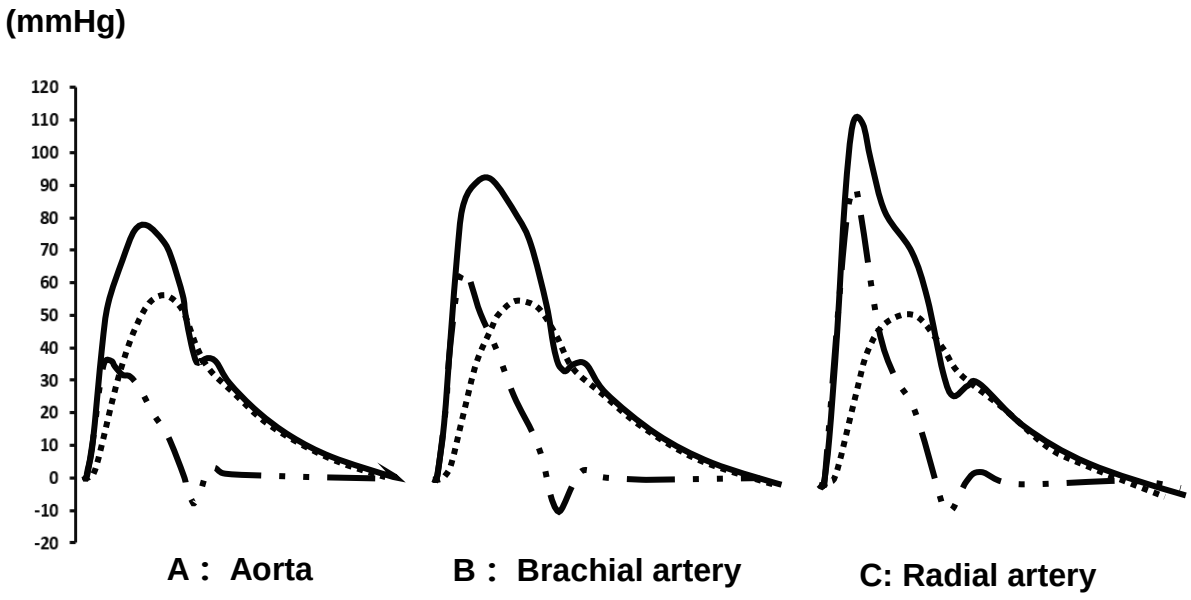


Figure 2.1 Ensemble averaged invasive A) aortic; B) brachial and C) radial arterial pressure waveforms (solid line) from a 53 year old female participant, with waveforms separated into reservoir pressure (····· , RP) and excess pressure (—·· , XSP) components. XSP increases stepwise from the aorta to the brachial and radial arteries, whereas RP does not appreciably change.

Associations of SBP and PP with reservoir-excess pressure. SBP was associated with RP (peak and integral) at all sites (r=0.662; 0.542; 0.551 between SBP and RP integral, r=0.821; 0.649; 0.708 between SBP and RP peak, at the aorta, brachial artery and radial artery respectively, Figure 2.2A). PP was associated with RP integral and RP peak at each site (r= 0.664; 0.559; 0.511 between PP and RP integral, and r= 0.869; 0.709; 0.738 between PP and RP peak at the aorta, brachial artery and radial artery respectively, Figure 2.2C). A significant difference in the regression slope between PP and RP peak from the aorta to the radial artery was observed (r=0.869; r=0.738; z=2.65; p=0.011). Conversely, both the correlations between SBP and PP with XSP peak increased significantly from the aorta to the radial artery (r=0.121; 0.508; z=3.04; p=0.004, r=0.294; 0.592; z=2.62; p=0.012, Figure 2.2B and D).

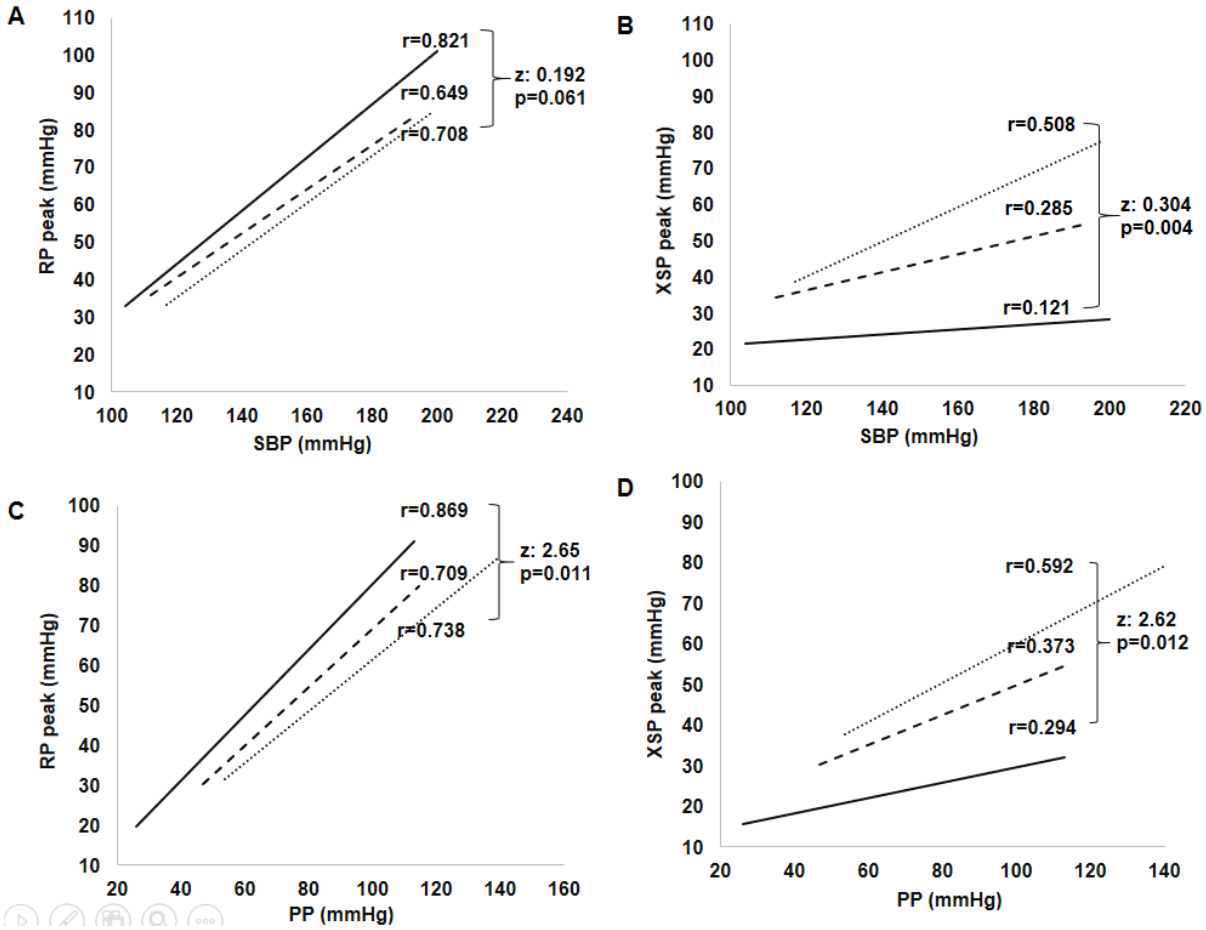


Figure 2.2 Associations between systolic blood pressure (SBP) and reservoir pressure (RP) peak (A); SBP and excess pressure (XSP) peak (B); pulse pressure (PP) and reservoir pressure (RP) peak (C); and PP and XSP peak (D). ——, at the aorta; – – –, at the brachial artery; ·····, at the radial artery. The Z scores and P values represent a comparison of the regression slope at the aorta vs radial artery.

2.5 Discussion

In this study, we sought to determine if RP and XSP are modified through large arteries of the human aorta to upper-limb, and whether this may help explain changes in BP. The principal finding was that the RP remained relatively uniform, and XSP was amplified from the ascending aorta to the brachial and radial arteries. Moreover, RP was the dominant component of the BP waveform at all arterial sites, and strongly associated with aortic SBP and PP. The contribution of XSP to total BP increased towards the periphery, suggesting a possible role in the increase in SBP and PP from central to peripheral arteries.

The reservoir-excess pressure concept was developed to overcome perceived limitations to a 'wave-only' model of arterial haemodynamics.[3] Parameters derived from this model independently predict cardiovascular events, mortality and markers of organ damage.[4, 5, 19] As a model, it also provides a physiologically reasonable description of BP waveform morphology,[41] with RP perhaps the principal BP component contributing to age-related increases in BP (specifically central BP augmentation).[68] Changes in local arterial properties (namely vessel stiffness) associated with ageing and disease can affect magnitude of SBP and PP amplification through the upper-limb,[69] but this variability in magnitude cannot be readily explained in terms of a wave-only approach.[70] The key finding of this study is that despite the peripheral amplification in SBP and PP, RP magnitude remained essentially unchanged. This is the first study to describe this phenomenon in the large arteries of the human upper-limb, although similar results (i.e. a relatively consistent RP) have been observed with progressive measurement of RP along the length of the human aorta.[63]

Mathematically, RP is 'pegged' to the mid-to-late diastolic (exponential) pressure decline [i.e. when in-flow (Q_{in}) = 0],[3] which remains somewhat consistent throughout the large arteries (exemplified in figure 2.1). This alone provides a reasonable explanation for the seemingly

uniform RP, and is in-line with the proffered physical basis of the reservoir-excess pressure concept. Indeed, RP is believed to consist of many smaller waves or wavefronts, that summate (average out) and propagate throughout the arterial system at the same speed as the measured BP.[40] Alternatively, taking an impedance-based viewpoint, the RP reflects a low-frequency component of BP, with a wavelength that spans the entire arterial system. Either way, the RP remains constant because its magnitude is probably dependent on global arterial compliance and net systemic resistance to outflow, rather than local arterial properties which determine the high-frequency components of BP (such as the XSP). There was a slight but not significant decrease in RP from the aorta to brachial and radial arteries. We speculate that this may be from greater stiffness and resistance in the peripheral vessels, thus leading to smaller injection of blood volume relative to the aorta.

If RP is constant throughout the large arteries, then BP amplification toward the periphery may be attributable to alterations in XSP. Certainly, the proportion of arterial pressure comprising XSP substantially increased peripherally (26.3% in the radial artery vs. 16.6% in the aorta), with XSP (peak and integral) being strongly associated with both SBP and PP at the radial artery. Underlying the peripheral amplification to XSP is likely a complex interplay between forward and reflected wave activity. Whilst the XSP has analogous features to the flow velocity trace in the proximal aorta,[3, 71] and thus consists predominantly of a forward wave component, the XSP composition is perhaps different in the periphery. Although sites of effective wave reflection in the human arterial system are unresolved in the literature,[72] the impedance mismatch in the periphery (that is replete with arterial branches and terminals) probably enhances reflected wave magnitude and contributes to amplified BP (and therefore the XSP) at the radial artery.

Despite the high local wave-reflection in the periphery, when forward traveling waves cross a mismatched site (or series of mismatched sites), net reflected wave energy may become dispersed,[73] or trapped,[74] because of a series of reflections and re-reflections. This creates an 'horizon effect' whereby discrete wave reflections generated in the periphery never return to the proximal aorta.[74] Indeed, Zambanini et al.[75] demonstrated by non-invasive wave intensity analysis that backward compression wave energy was higher at the radial artery, compared with the more central carotid artery. In that study, only 17% of forward compression wave energy was reflected at the carotid artery, but 27% was reflected at the radial artery. Extending this further, total arterial occlusion in the periphery (achieved by inflation of intra-arterial balloons, external BP cuffs or extra-arterial snares), generating an absolute reflection site, results in high wave reflection and increased BP locally, but unchanged augmentation of central BP (i.e. in the proximal aorta).[37, 76, 77] This provides a reasonable explanation as to why the RP (rather than XSP) has been found to dominate aortic BP waveform morphology and AIx centrally (RP comprised over 85% of the aortic BP waveform in the current study),[68, 70] and why RP was so highly related to aortic SBP and PP (see Figure 2.2a and c).

Firstly, this study was performed in a predominantly middle-to-older age male population with indications of coronary angiography and several comorbidities. Thus, our results may not be generalizable to individuals with different clinical characteristics. A number of participants were taking medications that could have altered reservoir characteristics (see table 2.1). However, the study was underpowered to determine if there was an effect of medication class on reservoir characteristics. We relied on a fluid-filled catheter system to measure intra-arterial BP in this study, and this may lead to measurement inaccuracy if the system is not handled correctly. However, we employed rigorous quality control steps for BP measurement as outlined in the methods section. Moreover, our findings are in-line with results of another study that used the gold-standard micro-tip pressure wires to derive RP along the length of the human

aorta,[63] and thus we consider that potential error arising from using a fluid-filled system was likely to be minimal. We also relied on pressure measurements alone to compute RP. Although the RP algorithm assumes zero-flow at the aortic root during diastole, we were unable to determine the effect of local flow oscillations on RP calculation.[78]

2.6 Conclusion.

This is the first study on arterial reservoir characteristics and BP physiology from the aorta to radial artery. Our results demonstrate that RP was the dominant component of the BP waveform within the large arteries, and strongly associated with aortic SBP and PP. Whilst the RP remained relatively uniform from the aorta to the brachial and radial arteries, the XSP increased towards the periphery alongside increases in SBP and PP. The reservoir-excess pressure concept therefore provides a physiologically plausible explanation for BP amplification through the human upper-limb, which may underlie the previously observed prognostic value of arterial reservoir characteristics.

2.7 Contribution of chapter 2 to thesis aims

Chapter 2 is the first study to explain BP amplification using the reservoir-excess pressure concept. The results of chapter 2 describe the contributory role of RP and XSP to the level of BP amplification from the aorta to the brachial and radial arteries. RP is the dominant component of the BP waveform and remains constant along large arteries. In contrast, XSP is gradually amplified, and the contribution to the BP amplification is increased. These findings are based on the direct measurement of reservoir pressure parameters using a catheter system, which is superior to non-invasive measurement. Thus, chapter 2 provides greater understanding on the underlying physiology of reservoir pressure parameters in the human large arteries and basic information for non-invasively estimating reservoir pressure parameters in the human upper-arm. Specifically, the relatively constant RP along large arteries implies that the non-

invasive measurement of RP at the brachial and radial artery would be highly concordant with aortic RP. Thus, intra-aortic (central) RP might be accurately estimated in the human upper-arm using a non-invasive cuff technique, and this is examined in chapter 4. However, the accurate measurement of reservoir pressure parameters relies on the accurate measurement of the BP waveform. Therefore, performance of the cuff device to estimate the central arterial BP waveform will be tested by comparison to the reference standard (radial tonometry) measures in chapter 3."

Chapter 3 - Comparison of central blood pressure estimated by a cuff-based device with radial tonometry

This thesis chapter has been published and formatted according to *American Journal of Hypertension.*

Peng X, Schultz MG, Abhayaratna WP, Stowasser M, Sharman JE. Comparison of central blood pressure estimated by a cuff-based device with radial tonometry. *American Journal of Hypertension.* 2016 Oct;29(10):1173-8.

Link to online article: https://www.ncbi.nlm.nih.gov/pubmed/27317573

doi: 10.1093/ajh/hpw063.

Citations: 6

Presentations:

- High Blood Pressure Research Council of Australia poster presentation, Melbourne, Australia, December 2015
- Association for Research into Arterial Structure and Physiology 15 congress poster presentation, Krakow, Poland, October 2015

3.1 Abstract

Objectives. New techniques that estimate central blood pressure (BP) using an upper arm cuff-based approach require performance assessment. The aim of this study was to compare a cuff-based device ($Cuff_{CBP}$) to estimate central BP indices [systolic BP, diastolic BP, pulse pressure (PP), augmentation pressure (AP), augmentation index (AIx)] with non-invasive radial tonometry (Ton_{CBP}). **Methods.** Consecutive $Cuff_{CBP}$ (SphygmoCor *Xcel*) and Ton_{CBP} (SphygmoCor 8.1) duplicate recordings were measured in 182 people with treated hypertension (aged 61±7 years, 48% male). Agreement between methods was assessed using standard calibration with brachial systolic BP and diastolic BP (measured with the *Xcel* device), as well as with brachial mean arterial pressure (MAP; 40% form factor method) and diastolic BP. **Results.** The mean difference±SD for systolic BP, diastolic BP, and PP between $Cuff_{CBP}$ and Ton_{CBP} were -0.89±3.48 mmHg (intra-class correlation [ICC] =0.98, p<0.001), -0.50±1.54 mmHg (ICC=0.99, p<0.001), and -0.42±3.57 mmHg (ICC=0.97, p<0.001), indicating good agreement. Wider limits of agreement were observed for AP and AIx (0.91±5.31 mmHg, ICC=0.75, p<0.001; -0.99±10.91%, ICC=0.75, p<0.001). Re-calibration with MAP and diastolic BP resulted in an overestimation of systolic BP with $Cuff_{CBP}$ compared with Ton_{CBP} (8.58±19.06 mmHg, ICC= 0.14, p=0.045). **Conclusion.** Central systolic BP, diastolic BP and PP derived from $Cuff_{CBP}$ are substantially equivalent to $Ton_{CBP,}$ although the level of agreement is dependent on calibration method. Further validity testing of $Cuff_{CBP}$ by comparison with invasive central BP will be required.

3.2 Introduction

Central blood pressure (BP) is associated with cardiovascular events and all-cause mortality independent of brachial BP,[80-83] and is recognised to be of pathophysiological, pharmacological and therapeutic interest.[84] Central BP can be measured non-invasively using several available methods, with the most widely published being radial tonometry. This technique enables derivation of a central (aortic) BP waveform from the radial BP waveform via application of a validated generalized transfer function.[85] Nonetheless, this device has not been widely utilised in routine clinical practice, in part due to operator-dependency and complexity of measurement. The potential clinical applicability of central BP estimation has improved recently with the development of a number of 'cuff-based' devices.[86] One such device, Sphygomocor *Xcel®,* (AtCor Medical, Sydney, Australia) records cuff brachial artery pressure waveforms at a BP lower than diastolic BP, and derives central BP via a brachial-to-aortic transfer function.

Estimation of central BP using the *Xcel* cuff-based device has been shown to be comparable to radial tonometry in one study comprising 30 healthy subjects.[56] Performance of the *Xcel* device among people with hypertension has not been undertaken, nor has the effect of different calibration methods been assessed, an issue that could have ramifications on accuracy of central BP estimation.[87] The aim of this current study was to compare central BP (systolic, diastolic and pulse pressure) and central BP waveform indices (augmentation pressure and augmentation index) estimated from the *Xcel* device ($Cuff_{CBP}$) with the radial tonometry method (Ton_{CBP}) in a large, well-characterised population of patients with hypertension, using 1) standard brachial systolic and diastolic BP for calibration, and 2) following re-calibration with brachial mean arterial pressure (MAP) and diastolic BP. Additionally, we sought to compare differences in estimated central BP indices when stratified by participant clinical characteristics including age, sex and antihypertensive medications. We hypothesised that the *Xcel* cuff-based device

measured central BP and central BP waveform indices would be substantially equivalent to the radial tonometry measures.

3.3 Methods

Study participants. Data from participants in the LOWCBP clinical trial (https://www.anzctr.org.au; ACTRN: 12613000053729) collected at baseline examination were analysed in this study. Participants were eligible if they had controlled clinic brachial BP (<140/90 mm Hg), were taking at least one but no more than three antihypertensive medications (in the past month), and if central systolic BP was ≥0.5 standard deviation above age- and gender-specific normal reference values.[69] Exclusion criteria included pregnancy or breastfeeding, concomitant therapy of angiotensin converting enzyme inhibitor and angiotension receptor blocker, or digoxin, lithium, non-depolarizing skeletal muscle relaxants, sex hormone or non-steroidal anti-inflammatory drugs. Individuals using any aldosterone inhibitor within 30 days of enrolment, had a contraindication to spironolactone therapy or diagnosed cardiovascular diseases were also excluded. A total of 182 participants with 359 matched, high-quality $Cuff_{CBP}$ and Ton_{CBP} recordings (177 recorded following 8 minutes and 182 following 10 minutes of seated rest respectively) were eligible for inclusion in this study. The study was approved by institutional Human Research Ethics Committees, and all participants provided written informed consent.

Study protocol. All participants attended clinic facilities for baseline assessment. Each participant was asked to refrain from consuming caffeine-containing products, cigarettes, alcohol, and to avoid heavy meals and exercise before the visit. Anthropometric measures were recorded prior to BP measurements. Following guideline recommendations,[84] seated BP measures were recorded using a correct cuff size supported at heart level. $Cuff_{CBP}$ and Ton_{CBP} measurements were recorded sequentially at 8 and 10 minutes following quiet seated rest.

Cuff$_{CBP}$. Cuff$_{CBP}$ central BP waveform indices were estimated by an oscillometric cuff-based device (Sphygomocor *Xcel,* AtCor Medical, West Ryde, Australia). Measurement involved the placement of a BP cuff on the upper-arm and automatic recording of standard oscillometric brachial BP, immediately after which the cuff automatically re-inflated to sub-diastolic pressure where it was held for a ten second period during which time a brachial artery waveform was captured. This brachial BP waveform was default calibrated with the brachial systolic BP and diastolic BP values as measured during the first inflation. A device specific brachial-aortic generalised transfer function (GTF) was then applied to derive a central BP waveform. Central pulse pressure (PP) was defined as the difference between central systolic BP and central diastolic BP. Central augmentation pressure (AP) was calculated as the difference between the second and the first systolic peaks (P2-P1). Central augmentation index (AIx) was defined as the ratio of AP to PP*100. The Cuff$_{CBP}$ estimated central systolic BP was also recalibrated using brachial MAP and diastolic BP applied to the exported digital waveform signal, with MAP calculated using a form factor equation, (0.4*PP + diastolic BP) as previously described.[87, 88] The quality of each measurement was evaluated by the system and only measures with acceptable quality were included.

Ton$_{CBP}$. Ton$_{CBP}$ central BP waveform indices were estimated immediately after each Cuff$_{CBP}$ measurement. A high-fidelity radial pressure sensor (SPC-301; Millar Instruments, Houston, TX) was used to applanate the radial artery, and a 10 second recording of the radial BP wave was captured to generate an ensemble average radial BP waveform. A GTF was then applied to derive a central BP waveform. Waveforms were calibrated firstly with brachial systolic and diastolic BP values measured by Cuff$_{CBP}$. Waveforms were also recalibrated using brachial MAP and diastolic BP as described for Cuff$_{CBP}$. Central BP waveform indices (PP, AP and AIx) were also calculated as described for Cuff$_{CBP.}$ The quality of the radial BP waveform was

evaluated by a built-in operator index, with only waveforms with an operator index >75 accepted in this study.

Statistical analysis. All data were analysed using SPSS for Windows software (version 22.0; SPSS Inc., Chicago, IL). $Cuff_{CBP}$ and Ton_{CBP} measures were compared using intra-class correlation coefficient (ICC) with absolute agreement. Linear regression was used to evaluate the relationship of measures of $Cuff_{CBP}$ and Ton_{CBP}. Bland-Altman analysis was performed to assess agreement and variability between $Cuff_{CBP}$ and Ton_{CBP}. Systematic bias was assessed from within Bland-Altman plots by Pearson correlation. Comparisons of the mean difference between Ton_{CBP} and $Cuff_{CBP}$ in subgroups were performed using independent-Samples T-test or one-way analysis of variance with a Z-statistic calculated to compare differences in regression slopes. $P<0.05$ was considered statistically significant.

3.4 Results

Clinical characteristics. The clinical characteristics of the study population are summarised in Table 3.1. As per our recruitment strategy, participants ranged widely in age from 27 to 73 and approximately half were men. On average, participants had slightly raised waist to hip ratio (WHR). The proportion of participants with diabetes was low, and the most common class of antihypertensive medication used was an angiotensin receptor blocker. The percentage of participants taking one, two or three antihypertensive medications was 42%, 38%, and 20%, respectively.

Table 3.1 Clinical characteristics of participants (n=182)

Variable	Mean ± SD or n (%)
Age (years)	61 ± 7
Sex (men %)	86 (48)
Waist:hip (ratio)	0.91 ± 0.10
Heart rate (bpm)	68 ± 11
Brachial systolic blood pressure (mm Hg)	128 ± 13
Brachial diastolic blood pressure (mmHg)	77 ± 9
Diabetes, n (%)	18 (14%)
Antihypertensive medications	
Diuretics, n (%)	24 (13%)
Beta blockers, n (%)	76 (42%)
Calcium channel blockers, n (%)	55 (30%)
Angiotensin converting enzyme inhibitors, n (%)	23 (13%)
Angiotensin receptor blockers, n (%)	106 (58%)
Vasodilators, n (%)	6 (0.03%)
Statin, n (%)	36 (20%)

Comparison of central BP indices derived from $Cuff_{CBP}$ and Ton_{CBP}. There was strong concordance between $Cuff_{CBP}$ and Ton_{CBP} central systolic BP, with a small mean difference and high correlation observed between measurements (Table 3.2 and Figure 3.1A). There was minimal variability observed in Bland-Altman analysis (Figure 3.1B), but evidence of slight systematic bias such that systolic cuff readings are systematically lower than radial tonometric readings as central systolic BP levels increased (Pearson r = -0.24, p<0.001). Similarly, there was a high correlation and a small mean difference between $Cuff_{CBP}$ and Ton_{CBP} central diastolic BP (Table 3.2), but with no evidence of systematic bias within Bland-Altman analysis (Pearson r = 0.047, p=0.37). A high correlation and a small mean difference in $Cuff_{CBP}$ and Ton_{CBP} central PP was observed (Table 3.2 and Figure 3.1C). Although there was a small standard deviation, a systematic bias (Pearson r = -0.40, p<0.001) was observed in Bland-Altman analysis (Figure 3.1D), such that pulse pressure cuff readings were systematically lower than radial tonometric readings as central pulse pressure levels increased. The correlation between $Cuff_{CBP}$ and Ton_{CBP} central AP was strong with a small mean difference (Table. 3.2). Although there was no systematic bias (Pearson r = 0.056, p=0.29), values were spread widely within Bland-Altman plots. The agreement between central AIx derived from $Cuff_{CBP}$ and Ton_{CBP} was good, with a small mean difference (Table 3.2 and Figure 3.1E) and no systematic bias within Bland-Altman plots (Pearson r = 0.036, p=0.492, Figure 3.1F).

Table 3.2 Comparison of central blood pressure parameters estimated by the cuff-based device and radial tonometry (n=359).

Variable	$Cuff_{CBP}$	$Tono_{CBP}$	Mean difference	ICC	Regression equation (y)	*P*-value
Central systolic blood pressure [a] (mmHg)	115.2 (11.5)	116.1 (12.3)	-0.9 (3.5)	0.977	1.0x - 2.5	< 0.001
Central diastolic blood pressure (mmHg)	77.5 (8.5)	78.0 (8.4)	-0.5 (1.5)	0.991	1.0x + 2.4	< 0.001
Central pulse pressure (mmHg)	37.7 (9.1)	38.1 (10.5)	-0.4 (3.6)	0.965	1.1x – 3.0	< 0.001
Central augmentation pressure (mmHg)	8.2 (6.4)	9.2 (6.7)	-0.9 (5.3)	0.749	0.7x + 3.4	< 0.001
Central augmentation index	21.1 (12.3)	22.1 (12.0)	-1.0 (10.9)	0.748	0.6x + 10.2	< 0.001
Central systolic blood pressure [b] (mmHg)	132.1 (14.9)	123.5 (13.3)	8.6 (19.1)	0.141	0.1x + 112.8	0.045

Data expressed as mean (SD). *P* value refers to ICC between devices. a: calibrated with brachial systolic blood pressure and diastolic blood pressure; b: calibrated with brachial mean arterial pressure and diastolic blood pressure. BP, blood pressure; PP, pulse pressure; AP, augmentation pressure; AIx, augmentation index; ICC, interclass correlations (Two-way mixed with absolute agreement); n, total number of measures recorded.

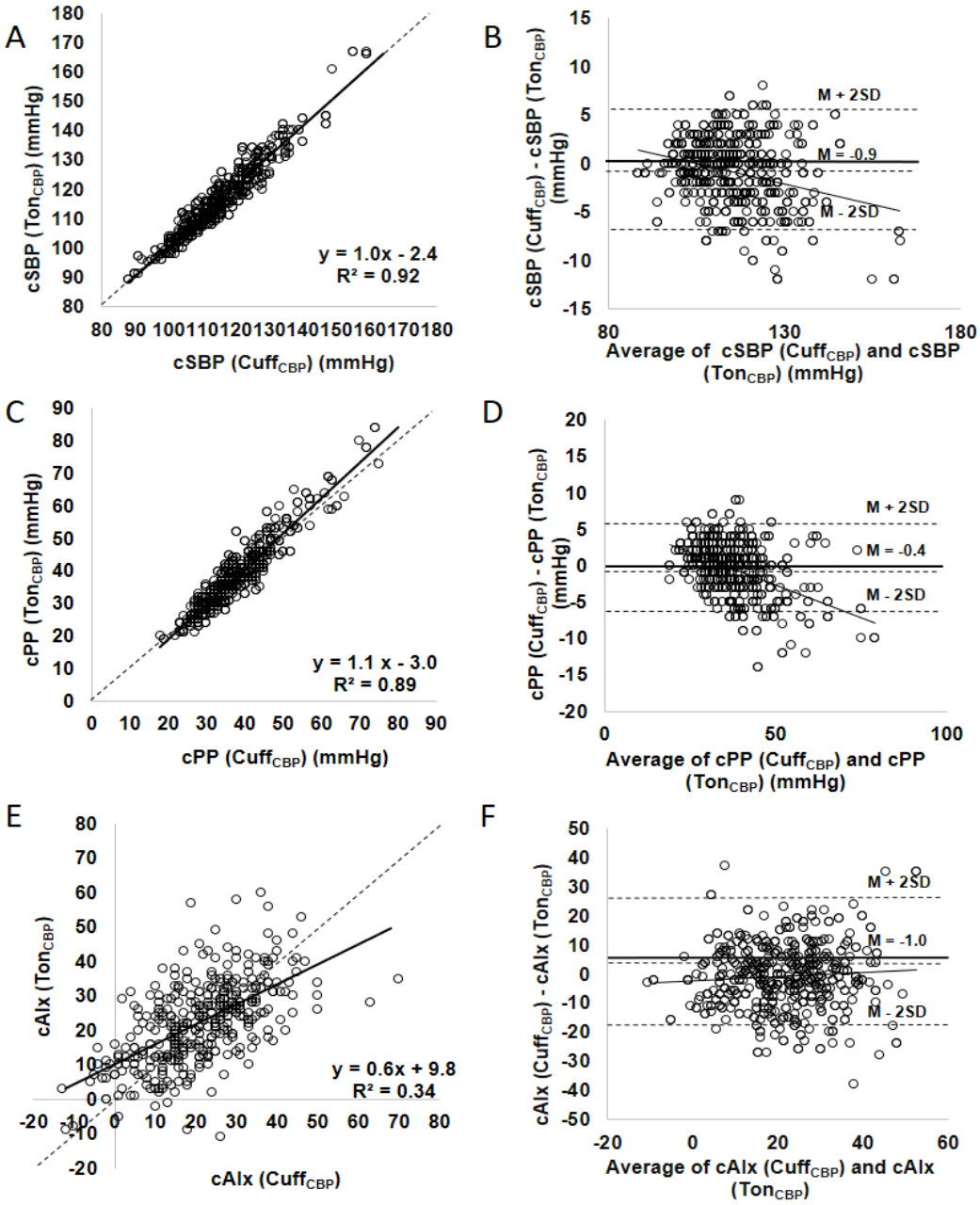
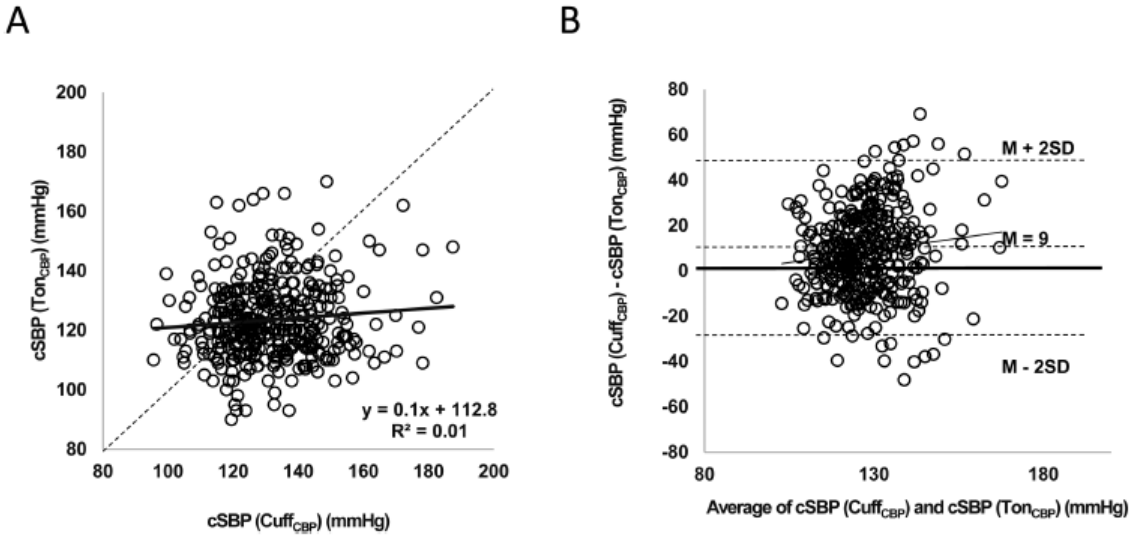


Figure 3.1 Concordance of central blood pressures estimated by the cuff-based device ($Cuff_{CBP}$) and radial tonometry (Ton_{CBP}) methods (n=359). Correlation of central systolic blood pressure (BP), central pulse pressure (PP), and central augmentation index (AIx) between two methods as A, C, E demonstrated respectively. The solid line is the trend line and the dashed line is the line of identity (n=359). A) Central systolic BP: $Cuff_{CBP}$ central systolic BP has a high agreement with $Tono_{CBP}$ central systolic BP with a small mean difference. C) Central PP: two central PPs were highly correlated with a small mean difference. E) Central AIx: the correlation of central AIxs between two devices was moderate. Mean difference of central systolic BP, central PP, and central AIx in the Bland-Altman analysis (B, D, and F, respectively). B) Central systolic BP: The minimal variability of central systolic BP was observed with some evidence of a systematic bias (Pearson r = -0.24, p<0.001). D) Central PP: a small standard deviation and a significant systematic bias (Pearson r = -0.40, p<0.001) was observed. F) Central AIx: the spread of central AIx was wide, and no evidence of systematic bias (Pearson r = 0.036, p=0.492). Abbreviation: M: mean; SD: standard deviation.



Comparison of central systolic BP derived by Cuff$_{CBP}$ and Ton$_{CBP}$ when recalibrated with brachial MAP and diastolic BP. Following recalibration with brachial MAP and diastolic BP, the central systolic BP using Cuff$_{CBP}$ overestimated the corresponding Ton$_{CBP}$ recalibrated central systolic BP. Values of recalibrated Cuff$_{CBP}$ and Tono$_{CBP}$ central systolic BP were not closely correlated (Table 3.2, Figure 3.2A) with a large spread of mean difference and evidence of slight systematic bias such that recalibrated systolic cuff readings were systematically higher than radial tonometric readings as central systolic BP levels increased (Pearson r = 0.117, $p<0.05$; Figure 3.2B).

Figure 3.2 Concordance of central systolic blood pressure (BP) estimated by the cuff-based device (Cuff$_{CBP}$) and radial tonometry (Ton$_{CBP}$) methods (n=359). Correlation of central systolic BP estimated by two devices A) The correlation of Cuff$_{CBP}$ central systolic BP and Ton$_{CBP}$ central systolic BP was low with a wide mean difference. The corresponding Bland-Altman plots of the mean values and differences between two devices B) The agreement of Cuff$_{CBP}$ central systolic BP and Ton$_{CBP}$ central systolic BP was low with a wide mean difference, and an evidence of systematic bias (Pearson r = 0.117, $p<0.05$). Abbreviation: M: mean; SD: standard deviation.

Comparison of central BP indices stratified according to participant characteristics. All analyses were repeated comparing central BP indices estimated by the two devices, stratifying patients according to sex (male/female), age (<60/>60 years), WHR (<0.90/>0.90 for male; <0.85/>0.85 for female), diabetes (yes/no), and anti-hypertensive medication type (diuretics, beta blocker, calcium channel blocker, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, vasodilators, statin). There were no significant differences in the agreement (mean difference) observed between all $Cuff_{CBP}$ and Ton_{CBP} central BP indices across all stratified comparisons, with the exception of central AIx, for which some significant differences were evident when grouped by anti-hypertensive medication type ($p<0.05$), and central PP, which was significantly different when stratifying according to age and WHR ($z=8.52$, $p<0.001$; $z=3.56$, $p<0.001$).

3.5 Discussion

In this study, we compared the performance of an oscillometric cuff-based device to estimate central BP and associated waveform indices by comparison to radial tonometry, which has been recommended as the non-invasive reference standard.[85] The results demonstrate that $Cuff_{CBP}$ estimated central BP and associated waveform indices are substantially equivalent to those derived from radial tonometry. The level of agreement for central systolic BP is however dependent on calibration method, and further research into the accuracy of central BP estimation by this new cuff-based device via comparison with invasive intra-arterial aortic BP should be undertaken.

Measurement of central BP via radial tonometry in clinical settings has not been widely accepted. Reasons for this include user-dependency, relative complexity and time required for accurate measurement.[86] In an attempt to overcome these issues, several cuff-based devices have been developed including the *Xcel* device, which is similar to conventional BP

measurement and should be familiar to patients and doctors. The performance of this device has only been assessed by comparison to radial tonometry in one smaller study (n=30) and our current work is in agreement by showing similar mean difference for central systolic BP (0.5±1.8 mmHg vs -0.9±3.5 mmHg), central diastolic BP (-0.01±0.5 mmHg vs -0.5±1.5 mmHg) and central AIx (1.8±7.0% vs -1.0±10.9%).[56] These data imply stability of the cuff-based device measures relative to radial tonometry. On the other hand, there was greater variability for central AIx, and the correlation of this variable between the two devices (Figure 1D) was less than for central systolic and diastolic BP despite the fact that there was no systemic bias between methods. Our finding is similar to that reported by Butlin et al.[56] and is probably related to the difficulty in reliably identifying the first systolic inflection point, which may be more challenging with the *Xcel* device that involves analysis of a volume displacement waveform.

The accuracy of central BP estimation can be influenced by calibration modes,[12, 13] but this current study, to our knowledge, is the first to explore variability in central BP after using two calibration methods of the *Xcel* cuff device. This is an important consideration because certain calibration modes have been shown to derive central BP values with stronger prognostic value for predicting end organ disease and clinical outcomes.[89, 90] The default calibration approach used predominantly (including with the *Xcel* device) is with non-invasive brachial systolic and diastolic BP. However, others have shown that peripheral waveforms calibrated with brachial MAP and diastolic BP derive central systolic BP values that are more comparable to invasively measured aortic systolic BP, when compared to standard calibration with brachial systolic BP and diastolic BP.[87, 91] This could be due to MAP and diastolic BP being relatively constant in conduit arteries,[88, 92] but also because modern oscillometric BP devices may be better at estimating true (intra-arterial) MAP than systolic BP. In this study, Ton_{CBP} estimated central systolic BP was significantly higher when radial waveforms were recalibrated using brachial

MAP and diastolic BP (from 116.1 mmHg to 123.5 mmHg). This is not unexpected and in agreement with others,[87, 93] but much greater increases in central systolic BP were observed when $Cuff_{CBP}$ was recalibrated with brachial MAP and diastolic BP (from 115.2 mmHg to 132.1 mmHg). This difference is probably related to waveform shape discrepancies between radial tonometric compared with brachial oscillometric waveforms. Indeed, from proximal to peripheral arteries there is amplification of systolic BP with the radial wave shape tending to have a higher and narrower systolic peak than proximal waveforms.[93, 94] Therefore, applying the same form factor for both radial and brachial waveforms (i.e. 40%) may result in a relatively higher derived central systolic BP from the brachial waveform. More investigation is required to refine calibration techniques of the cuff-based device (also taking into consideration demographic characteristics such as body habitus) to ensure accurate central BP estimation by comparison to intra-arterial aortic BP.

This study was conducted in a specific clinical trial population of people with controlled hypertension and relatively high central systolic BP compared to brachial systolic BP, thus our results may not be generalizable to other populations. Secondly, the performance of central BP estimated by an upper-arm cuff-based device was compared with radial tonometry, as opposed to an invasive gold standard.

3.6 Conclusion.

Central BP derived from $Cuff_{CBP}$ is substantially equivalent to Ton_{CBP} using the standard calibration method of brachial systolic and diastolic BP. The lower inter-device agreement of central systolic BP following recalibration and systematic biases observed in central pulse pressure estimation indicate that further refinement in calibration strategy may be useful for deriving more accurate estimates of central BP, and invasive comparison studies will be required for this step.

3.7 Contribution of chapter 3 to thesis aims

Chapter 3 is the first to report the performance of central BP estimated by a non-invasive cuff BP device (Xcel, AtCor Medical) by comparison to radial tonometry (the non-invasive reference standard) in a large population. The principal finding was that central BP estimated using the cuff-based device was substantially equivalent to those derived by the radial tonometry. The results indicate that the cuff device may be useful to derive estimates of either central or brachial reservoir pressure parameters. Altogether, chapter 4 determines whether reservoir pressure parameters can be derived from either cuff measured brachial BP waveforms or estimated central BP waveforms. This will be determined by comparison of cuff measures with invasive gold standard measures of intra-aortic BP waveforms.

Chapter 4 - Non-invasive measurement of reservoir pressure parameters from brachial-blood pressure waveforms

This thesis chapter has been published and formatted according to *Journal of Clinical Hypertension.*

Peng X, Schultz MG, Picone DS, Dwyer N, Black JA, Roberts-Thomson P, Sharman JE. Non-invasive measurement of reservoir pressure parameters from brachial-cuff blood pressure waveforms. *Journal of Clinical Hypertension.* 2018 Dec:20(12):1703-1711.

doi: 10.1111/jch.13411.

Presentations:

- ARTERY 15 congress poster presentation, Krakow, Poland, October 2015
- Pulse of Asia moderated poster presentation, Seoul, South Korea, September 2016 - Outstanding presenter was awarded for this presentation.

4.1 Abstract

Reservoir pressure parameters [eg, reservoir pressure (RP) and excess pressure (XSP)] are biomarkers derived from blood pressure (BP) waveforms that have been shown to predict cardiovascular events independent of conventional cardiovascular risk markers. However, whether RP and XSP can be derived non-invasively from operator-independent cuff device measured brachial or central BP waveforms has never been examined. This study sought to achieve this by comparison of cuff reservoir pressure parameters with intra-aortic reservoir pressure parameters. 162 participants (aged 61±10 years, 72% male) undergoing coronary angiography had the simultaneous measurement of cuff BP waveforms (via SphygmoCor XCEL, AtCor Medical) and intra-aortic BP waveforms (via fluid-filled catheter). RP and XSP calculated from the cuff measured brachial BP waveform and estimated central BP waveform, were compared with intra-aortic measures. The strength of concordance between cuff measured and intra-aortic reservoir pressure parameters were defined based on intra-class correlation coefficients (ICC). Concordance between brachial-cuff and intra-aortic measurement was moderate-to-good for RP peak (36±11 vs 48±14 mm Hg, $P < 0.001$; ICC 0.77, 95% CI: 0.71-0.82), and poor-to-moderate for XSP peak (28±10 vs 24 ± 9 mm Hg, $P < 0.001$; ICC 0.49, 95% CI: 0.35-0.60). Concordance between central-cuff and intra-aortic measurement was moderate-to-good for RP peak (35±9 vs 46±14 mm Hg, $P < 0.001$; ICC 0.77, 95% CI: 0.70-0.82), but poor for XSP peak (12 ± 3 vs 24 ± 9 mm Hg, $P < 0.001$; ICC 0.12, 95% CI: −0.13 to 0.31). In conclusion, both brachial-cuff and central-cuff methods can reasonably estimate intra-aortic RP, whereas XSP can only be acceptably derived from brachial-cuff BP waveforms. This should enable widespread application to determine the clinical significance, but there is significant room for refinement of the method.

4.2 Introduction

High blood pressure (BP) is the leading contributor to the global burden of disease.[27] Many investigators have proposed that useful clinical biomarkers may be derived from analysis of arterial BP waveforms.[33] One such construct is the reservoir-excess pressure model in which the arterial BP waveform is theorized to represent the sum of a reservoir pressure (RP, determined by global systemic compliance and resistance) and an excess pressure (XSP, related to local wave travel).[3] Reservoir pressure parameters (RP, XSP and the associated systolic rate constant) derived from non-invasively acquired BP waveforms (e.g. via carotid or radial tonometry) predict cardiovascular events independent of conventional cardiovascular risk factors.[4, 6, 24] However, these modes of BP waveform acquisition are technically challenging, which limits widespread application of non-invasively derived reservoir pressure parameters.

Technological advancements now allow recording of brachial BP waveforms and estimation of central BP using a standard operator-independent, oscillometric BP cuff method that enables the analysis of brachial and central reservoir pressure parameters. Altogether, the cuff approach could be useful for more widespread measurement of reservoir pressure parameters, but it has not been tested before. Therefore, this study aimed to determine whether reservoir pressure parameters could be derived non-invasively from cuff acquired brachial or central BP waveforms. We sought to achieve this by comparison of reservoir pressure parameters derived non-invasively from cuff measured brachial and central BP waveforms with invasively recorded aortic reservoir pressure parameters.

4.3 Methods

Participants. 239 patients scheduled for diagnostic coronary angiography at the Royal Hobart Hospital (Hobart, Australia) were screened for participation in this study. Exclusion criteria included participants with atrial fibrillation, aortic stenosis, or waveform data of insufficient

quality. Complete data from 162 participants were included for the analysis of brachial-cuff measurement, and 151 participants for the analysis of central-cuff measurement. The description of participant flow and quality control is provided in figure 4.1. The study was approved by the University of Tasmania Human Research Ethics Committee, all participants provided written consent, and all research was carried out in accordance with the Declaration of Helsinki.

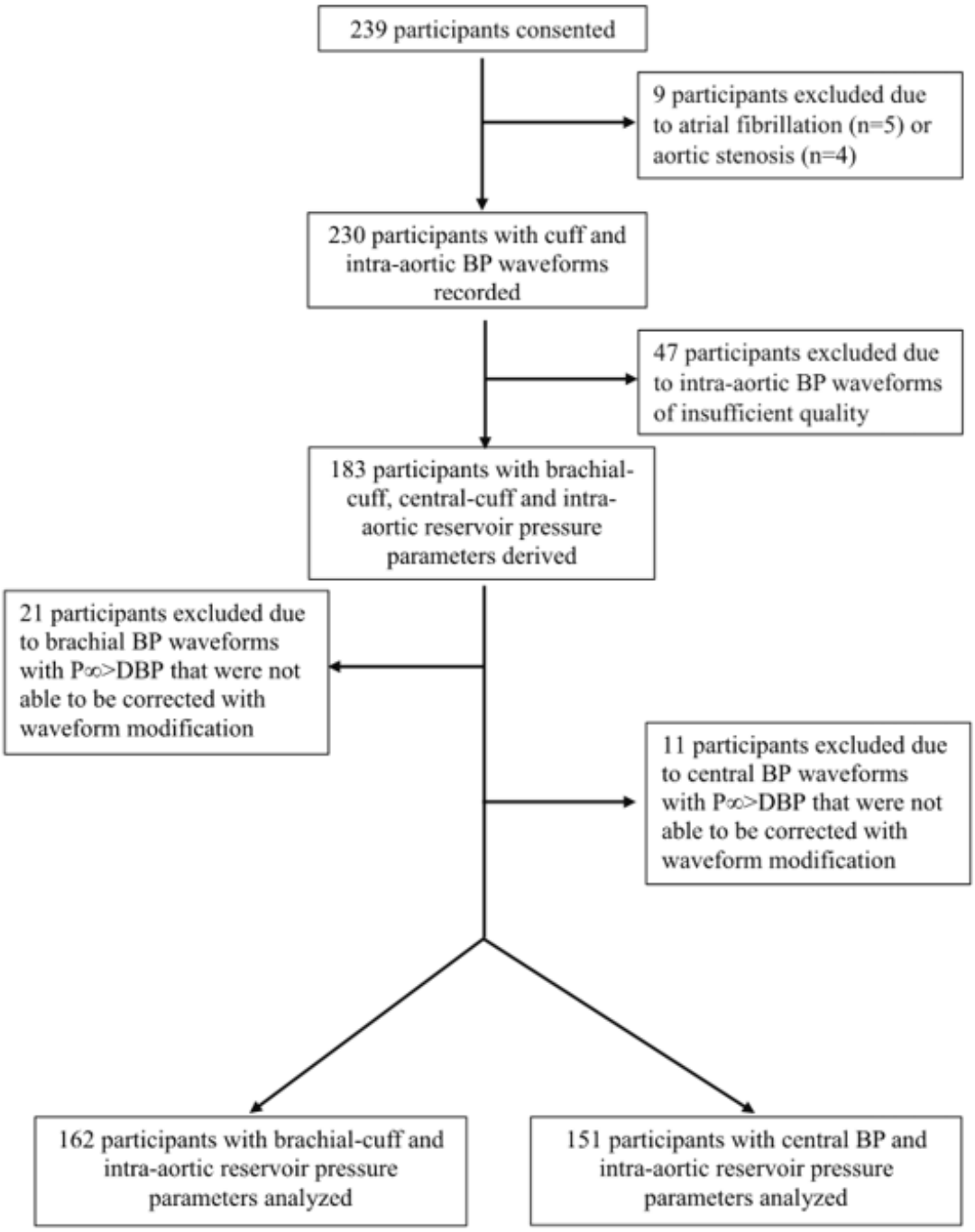


Figure 4.1 Participant flow diagram. The P∞ was found to be >DBP during derivation of reservoir pressure parameters among several cuff BP waveforms. This occurred due to a small upstroke at end diastole that was an artifact of ensemble averaging of the BP waveforms and is non-physiological (see Protocol in Methods). The anomaly was corrected by removal of the small upslope occurring at end diastole and then re-applying the algorithm to derive reservoir pressure parameters. This correction was not possible in brachial-cuff BP waveforms from 21 participants or in central BP waveforms from 11 participants, and thus were excluded from analysis (representing 18% of available participants). BP, blood pressure; P∞, pressure infinite; DBP, diastolic blood pressure

Protocol. Patients were prepared for coronary angiography in accordance with standard clinical care. All study measurements were obtained in the supine position under stable haemodynamic conditions and prior to the clinical procedure. The brachial-cuff waveforms were measured via an oscillometric BP device, simultaneously with intra-aortic BP waveforms that were continuously recorded at the ascending aorta via a fluid-filled catheter. The central BP waveforms were estimated from the cuff device measured brachial BP waveforms via a generalised transfer function (GTF), thus central-cuff BP waveforms were simultaneously acquired to the recording of intra-aortic BP waveforms. The non-invasive cuff and intra-aortic BP waveform measurements were performed in duplicate on the majority of participants (i.e. 73%), with the remaining only having one recording. The total time to complete each study was approximately three minutes. Reservoir pressure parameters were derived from the measured BP waveforms, and brachial-cuff and central-cuff reservoir pressure parameters were respectively compared with intra-aortic reservoir pressure parameters. Quality control measures conducted on BP waveforms were: 1) inconsistent intra-aortic BP waveforms caused by the issues that arose during the procedure, such as participant or catheter was unexpectedly moved, were excluded; 2) non-invasive cuff BP waveforms having P∞> diastolic BP were excluded as this is the result of an artefact of ensemble averaging BP waveforms without time gating, and is non-physiological.

Cuff BP waveform measurement. Cuff BP waveforms were measured using a SphygmoCor Xcel device (Atcor Medical, Sydney, Australia) with an appropriately sized cuff positioned on the left upper arm level with the right atrium. The device first measures brachial BP using a validated oscillometric algorithm (Medical model 222, Sun Tech Medical Inc. Morrisville, USA),[95, 96] and then re-inflates to a sub-diastolic BP (10 mmHg below diastolic BP), at which point 5 seconds of brachial volume displacement waveforms were recorded simultaneously with intra-aortic BP waveforms. The brachial-cuff volumetric waveforms were ensemble

averaged offline, with the peak and nadir calibrated to oscillometric brachial systolic and diastolic BP respectively. The central-cuff BP waveforms were automatically estimated from the ensemble averaged brachial-cuff BP waveforms with an application of a built-in GTF. These brachial-cuff and central-cuff BP waveforms were used to derive reservoir pressure parameters using a customised algorithm.

Intra-aortic BP waveform measurement. Intra-aortic BP waveforms were acquired using 5Fr and 6Fr fluid-filled catheters inserted via the radial artery and positioned within the ascending aorta, approximately 5 cm distal to the aortic valve (position confirmed by fluoroscopy). The catheter system was flushed prior to continuous BP waveform acquisition. BP signals were recorded via an analogue-to-digital signal converter (Lab view, AD Instruments, Bella Vista, Australia) within LabChart 7 software (AD Instruments, Bella Vista, Australia). 5 seconds of consistent aortic BP signals (corresponding precisely to the time of brachial-cuff BP waveform acquisition) were extracted and calibrated offline using a 2-point method to convert units of measurement from Volts to mmHg as previously described.[9] The calibrated BP waveforms were ensemble averaged to derive reservoir pressure parameters. The dynamic response (frequency and damping) of the fluid-filled system was assessed by performing 'pop' tests, and confirmed in the appropriate range as outlined by Gardner[10] (frequency>18 Hz and damping coefficient>0.3).

Derivation of reservoir pressure parameters. The customised Matlab program to derive reservoir pressure parameters has previously been described.[4] RP was calculated using the pressure-only approach as per equation 4.1.[6, 39, 48]

$$\frac{\mathbf{dP_{reservoir}}}{\mathbf{dt}} = \mathbf{Sc}(\mathbf{P} - \mathbf{P_{reservoir}}) - \mathbf{Dc}(\mathbf{P_{reservoir}} - \mathbf{P}\infty)$$

Equation 4.1 Calculation of reservoir pressure.

XSP was calculated by subtracting RP from total pressure. The systolic and diastolic rate constants of the system are Sc and Dc respectively, and represent the rate constants relating to the speed of upstroke and downstroke of the BP waveform.[6] Sc=1/ZC (Z is a constant which will depend upon a number of factors, such as the local wave speed and cross-sectional area at the root of the aorta, and C is the compliance of the whole arterial tree), Dc = 1/RC (R is the effective resistance of the peripheral systemic circulation), P is measured total pressure, $\bar{P}$ is reservoir pressure, and $P\infty$ is the arterial asymptotic pressure. Figure 4.2 represents a BP waveform with example reservoir pressure components.

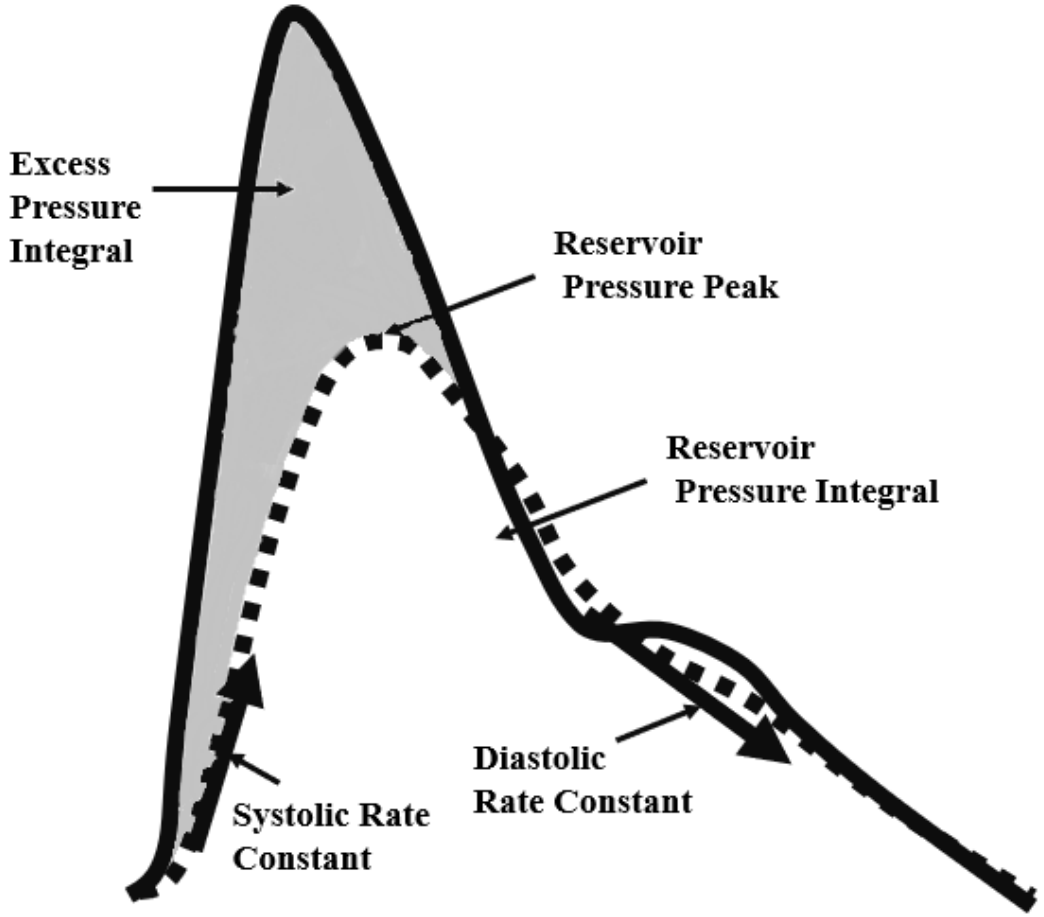


Figure 4.2 Blood pressure waveform (———) with example reservoir pressure parameters. The reservoir pressure (·····) and excess pressures (in shadow) are expressed as peak and integrals (area under the pressure curves).

Statistical analysis. All data were analysed using SPSS (version 22.0; SPSS Inc., Chicago, IL). Concordance between non-invasive cuff and intra-aortic reservoir pressure parameters was assessed based on: 1) consistency determined by intra-class correlation coefficients (ICC) using a single rater measurement, consistency, 2-way mixed-effects model; 2) mean difference tested by paired T-test, and; 3) variability in mean differences examined by Bland-Altman. The strength of consistency between measurements was defined from ICC and 95% confidence intervals (95%CI) as: <0.50 poor; 0.50 to 0.75 moderate; 0.75 to 0.90 good; and 0.90 to 1.0 excellent, according to Koo and Li.[97] Systematic bias was assessed from within Bland-Altman plots by Pearson correlation and the Z-statistic. $p<0.05$ was considered statistically significant.

4.4 Results.

Clinical characteristics. Participants were predominantly male and middle-to-older aged, with a high prevalence of a history of high BP and currently taking antihypertensive medications (Table 4.1). Kidney function (as determined from estimated glomerular filtration rate) was slightly reduced on average and almost two thirds of participants had a significant stenosis in one or more coronary artery.

Table 4.1 Clinical characteristics of study participants (n=162).

Variable	**Mean (SD) or n (%)**
Age (years)	61 (10)
Sex (men %)	116 (72)
Body mass index ($kg \cdot m^{-2}$)	28 (7)
History of high BP (≥140/90 mmHg) n (%)	151 (93)
eGFR (mL/min/1.73 m^2)	77 (26)
Diabetes n (%)	38 (24)
Smoking n (%)	35 (22)
Antihypertensive medication n (%)	138 (86)
Lipid profile ($mmol \cdot L^{-1}$)	
High-density lipoprotein cholesterol	0.8 (0.4)
Low-density lipoprotein cholesterol	1.9 (0.8)
Triglycerides	1.5 (0.7)
Angiographic findings n (%)	
No significant stenosis	57 (36)
Single-vessel disease	33 (21)
Double-vessel disease	42 (27)
Multi-vessel disease	25 (16)

A history of high blood pressure (BP) was determined from the participant's medical records. Significant stenosis was defined by ≥ 50% occlusion. eGFR, estimated glomerular filtration rate.

Comparison between brachial-cuff and intra-aortic reservoir pressure parameters. There was a small difference between brachial-cuff and intra-aortic systolic BP (128±16 mmHg vs 126 ±19 mmHg, p=0.17), whereas brachial-cuff diastolic BP was significantly higher than intra-aortic diastolic BP (73±9 mmHg vs 65±10 mmHg, p<0.001). Figure 4.3 shows example waveforms to illustrate the difference of reservoir pressure parameters derived from brachial-cuff and intra-aortic BP waveforms. Table 4.2A presents the comparisons between brachial-cuff and intra-aortic reservoir pressure parameters. There was moderate-to-good consistency for RP peak, but with significant mean difference and systematic bias indicating a trend for greater underestimation of intra-aortic RP peak by brachial-cuff measurement at higher RP peak (figure 4.4A and 4.4B). Similarly, for the RP integral, there was moderate consistency, a significant mean difference, and systematic bias for greater underestimation with increasing values (r=-0.69, p<0.001). For XSP peak, there was poor-to-moderate consistency and a significant overestimation without evidence of systemic bias (figure 4.4C and 4.4D). There were similar findings for XSP integral. For the systolic and diastolic rate constants, there was poor-to-moderate and poor consistency, respectively. There was significant mean difference and evidence of systematic bias for both rate constants (systolic r=0.51 and diastolic r=0.54, p<0.001 both).

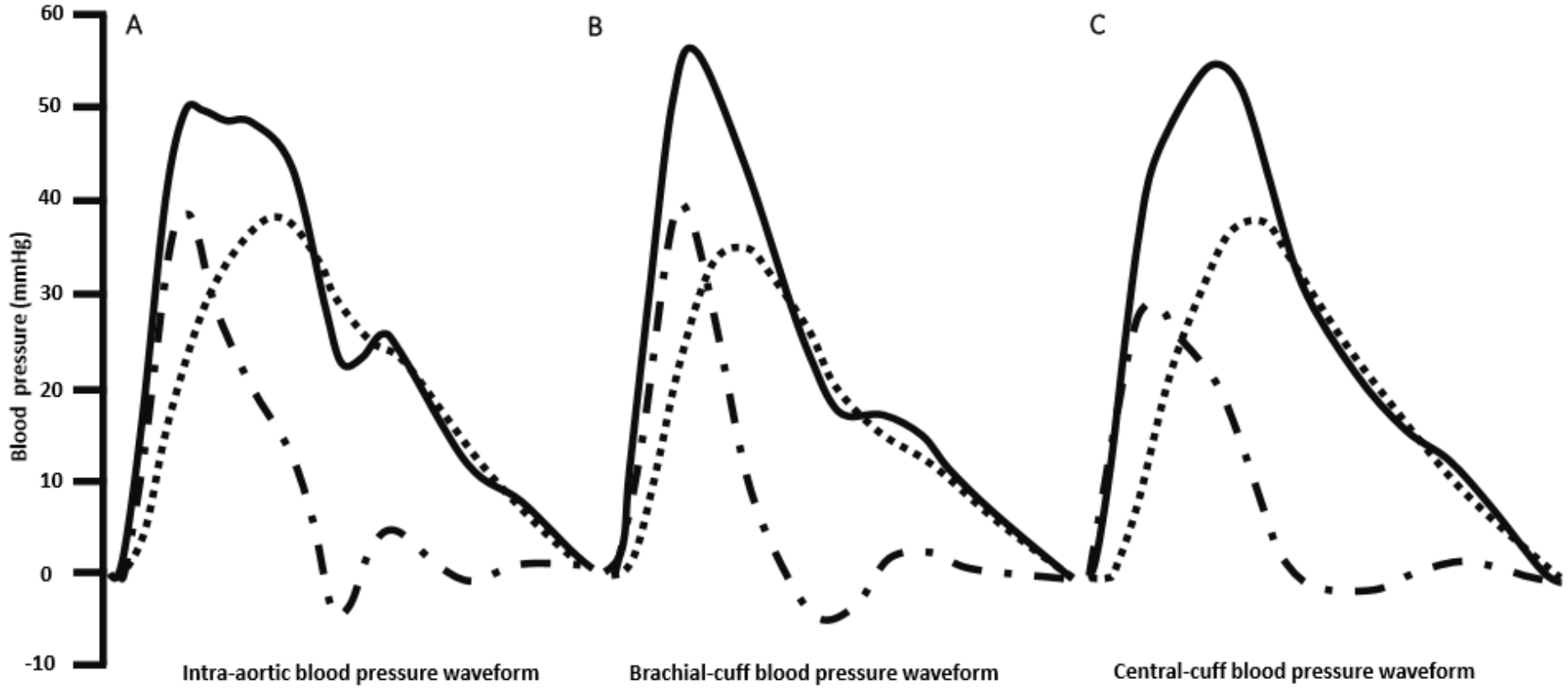


Figure 4.3 Ensemble averaged A) intra-aortic B) brachial-cuff and C) central-cuff blood pressure waveforms (———) separated into reservoir (····· , RP) and excess pressure (— · — , XSP) components from a 63 year old female participant. Waveforms have been rescaled so that diastolic blood pressure is equal to 0.

Table 4.2 Comparison between brachial-cuff and intra-aortic reservoir pressure parameters (n=280).

Parameters	Brachial-cuff mean (SD)	Intra-aortic mean (SD)	Cuff-aortic mean difference (SD)	p-value	ICC (95% CI)	Regression equation (y)
RP peak, mmHg	36 (11)	48 (14)	-12 (1)	<0.001	0.77 (0.71, 0.82)	-0.32x + 1.59
RP integral, mmHg·s^{-1}	10 (3)	18 (6)	-8 (4)	<0.001	0.66 (0.57, 0.73)	-0.81x + 3.69
XSP peak, mmHg	28 (10)	24 (9)	5 (1)	<0.001	0.49 (0.35, 0.60)	0.16x + 0.77
XSP integral, mmHg·s^{-1}	5 (2)	4 (2)	1 (2)	0.003	0.60 (0.49, 0.68)	0.11x + 1.57
Systolic rate constant, s^{-1}	0.1537 (0.0948)	0.1713 (0.0699)	-0.0176 (0.0070)	0.013	0.39 (0.23, 0.52)	0.51x - 0.11
Diastolic rate constant, s^{-1}	0.0385 (0.0355)	0.0227 (0.0128)	0.0157 (0.0023)	<0.001	0.03 (-0.22, 0.24)	0.54x - 0.01

RP, reservoir pressure; XSP, excess pressure; SD, standard deviation; p value is for the comparison between brachial-cuff and intra-aortic reservoir pressure parameters. ICC, interclass correlations with a single rater measurement, consistency, 2-way mixed-effects model; CI, confidence interval. Regression equation is the trend of systemic bias in the Bland-Altman analysis.

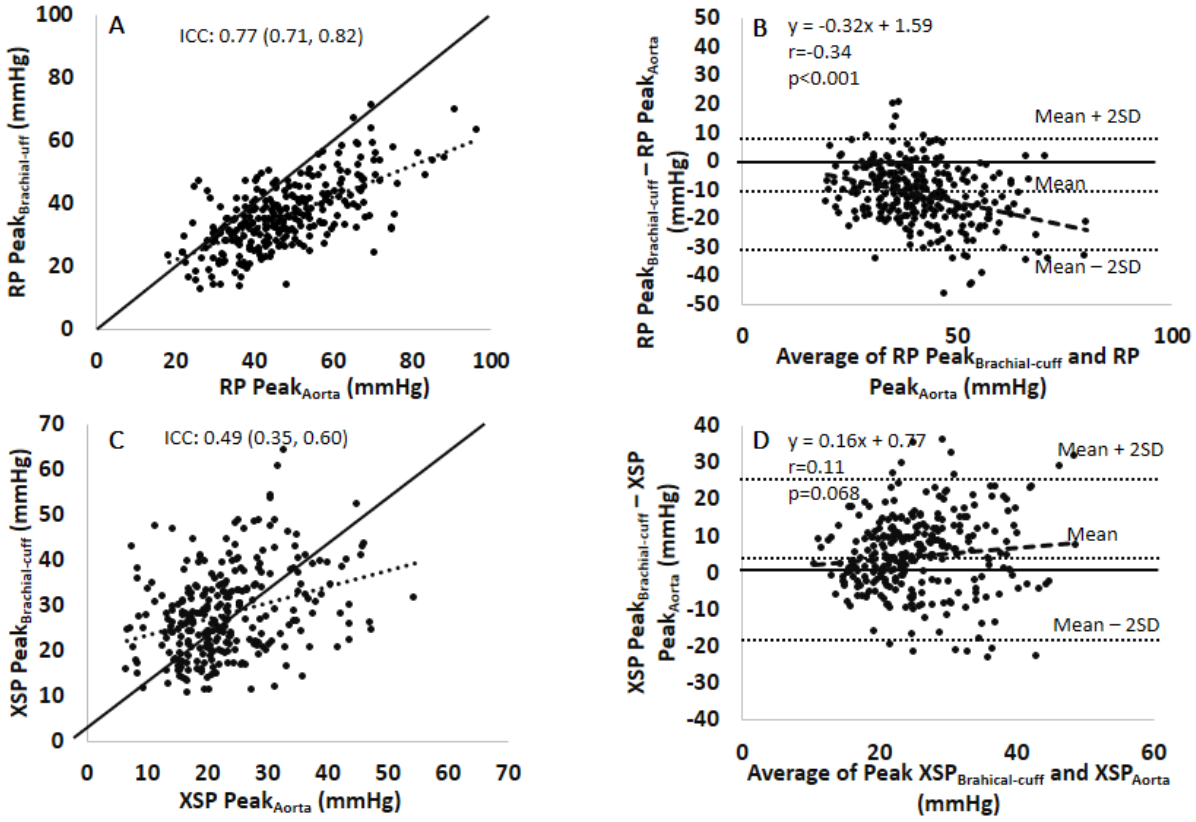


Figure 4.4 Comparisons of brachial-cuff and intra-aortic blood pressure waveform derived reservoir pressure (RP) and excess pressure (XSP) (n=280). ——— is the line of identity, ····· is the trend line, – – is the systematic bias line within Bland-Altman analysis. Intra-class correlation coefficients and Bland-Altman plots of the reliability between brachial-cuff and intra-aortic RP peak (A and B), and between brachial-cuff and intra-aortic XSP peak (C and D), respectively. Abbreviation: ICC: intra-class correlation; SD: standard deviation. r: Pearson correlation. p value is for the comparison of systematic bias with identity line within Bland-Altman plots.

Comparison between central-cuff and intra-aortic reservoir pressure parameters. Central-cuff systolic BP was significantly lower than intra-aortic systolic BP (116 ±14 mmHg vs 125±18mmHg, p<0.001). Conversely, central-cuff diastolic BP was higher than intra-aortic diastolic BP (74±10 mmHg vs 65±10 mmHg, p<0.001). Figure 4.3 shows example waveforms to illustrate the difference of reservoir pressure parameters derived from central-cuff and intra-aortic BP waveforms. Table 4.2B presents the comparisons between central-cuff and intra-aortic reservoir pressure parameters. There was moderate-to-good consistency for RP peak, but with significant mean difference and systematic bias indicating a trend for greater underestimation of intra-aortic RP peak by central-cuff measurement at higher RP peak (figure 4.5A and 4.5B). Similarly, for the RP integral, there was moderate consistency and a significant mean difference with systematic bias for greater underestimation as RP integral increases (r=-0.64, p<0.001). However, for XSP peak, XSP integral, systolic rate constant and diastolic rate constant, the consistencies were poor, and mean differences were significant with evidences of systemic bias (r=-0.81 for XSP peak, figure 4.5C and 4.5D; r=-0.82 for XSP integral; r=-0.30 for systolic rate constant; and r=-0.29 for diastolic rate constant, respectively; and all p<0.001).

Table 4.3 Comparison between central-cuff and intra-aortic reservoir pressure parameters (n=262).

Parameters	Central-cuff mean (SD)	Intra-aortic mean (SD)	Cuff-aortic mean difference (SD)	p-value	ICC (95% CI)	Regression equation (y)
RP peak, mmHg	35 (9)	46 (14)	-11 (10)	<0.001	0.77 (0.70, 0.82)	-0.52x + 9.72
RP integral, mmHg·s^{-1}	11 (3)	17 (6)	-6 (4)	<0.001	0.67 (0.58, 0.74)	-0.73x + 4.41
XSP peak, mmHg	12 (3)	24 (9)	-12 (9)	<0.001	0.12 (-0.13, 0.31)	-1.53x + 15.06
XSP integral, mmHg·s^{-1}	2 (1)	4 (2)	-1 (2)	<0.001	0.23 (0.01, 0.39)	-1.45x + 2.89
Systolic rate constant, s^{-1}	0.2307 (0.0497)	0.1655 (0.0677)	0.0652 (0.0818)	<0.001	0.10 (-0.16, 0.29)	-0.57x + 0.18
Diastolic rate constant, s^{-1}	0.0377 (0.0117)	0.0228 (0.0157)	0.0109 (0.0184)	<0.001	0.21 (0.00, 0.39)	-0.51x + 0.03

RP, reservoir pressure; XSP, excess pressure; SD, standard deviation; p value is for the comparison between central-cuff and intra-aortic reservoir pressure parameters. ICC, interclass correlations with a single rater measurement, consistency, 2-way mixed-effects model; CI, confidence interval. Regression equation is the trend of systemic bias in the Bland-Altman analysis.

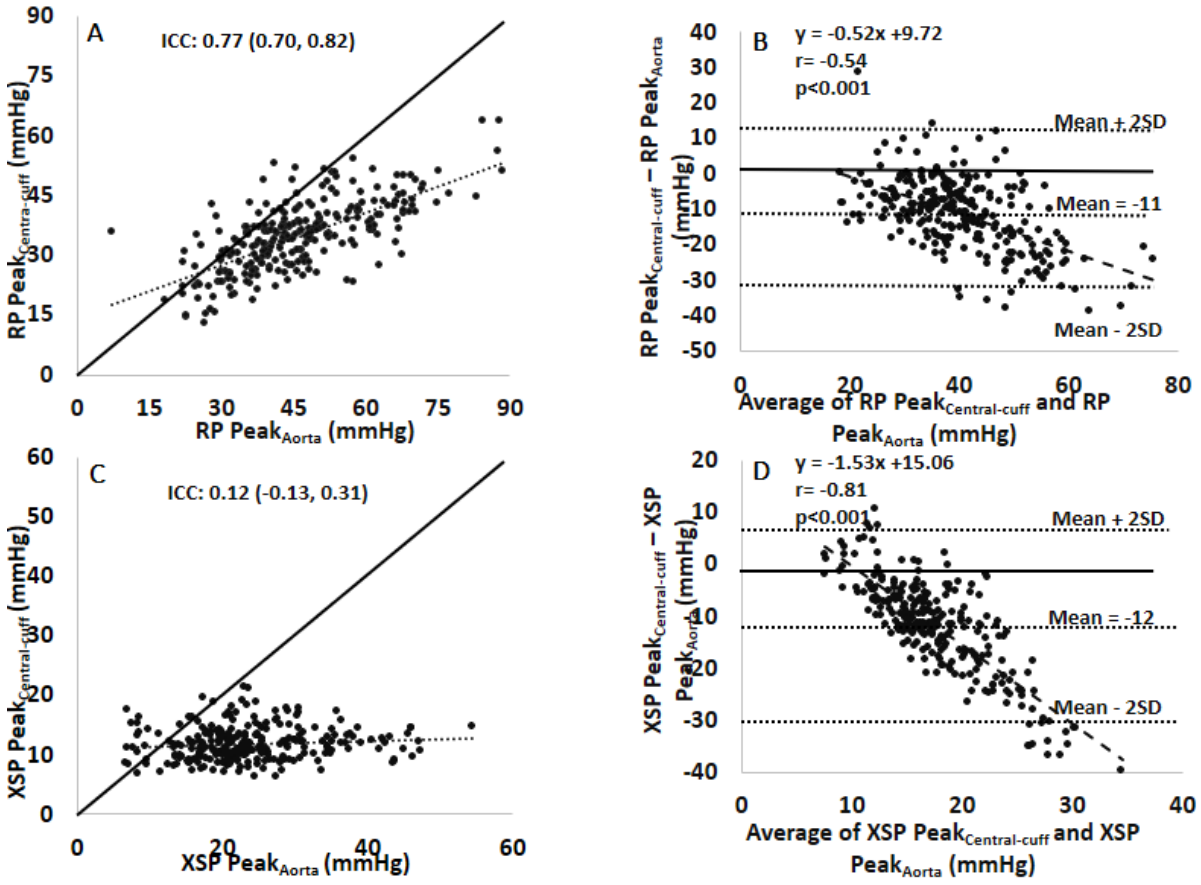


Figure 4.5 Comparisons of central-cuff and intra-aortic blood pressure waveform derived reservoir pressure (RP) and excess pressure (XSP) (n=280). ——— is the line of identity, ····· is the trend line, – – is the systematic bias line within Bland-Altman analysis. Intra-class correlation coefficients and Bland-Altman plots of the reliability between brachial-cuff and intra-aortic RP peak (A and B), and between brachial-cuff and intra-aortic XSP peak (C and D), respectively. Abbreviation: ICC: intra-class correlation; SD: standard deviation. r: Pearson correlation. p value is for the comparison of systematic bias with identity line within Bland-Altman plots.

4.5 Discussion.

In this study, we demonstrate that it is practically feasible to derive some reservoir pressure parameters from non-invasively acquired cuff BP waveforms, albeit with variable reliability when compared with intra-aortic reservoir pressure parameters. Intra-aortic RP was reasonably measured from the cuff-based device measured brachial and central BP waveforms, whereas the brachial-cuff method more reliably estimated intra-aortic XSP than the central-cuff method. Neither of the two cuff waveforms were acceptable in terms of generating accurate estimation of the systolic and diastolic rate constants. These findings imply that the brachial-cuff method may be more applicable in future work to determine the clinical importance of RP and XSP when compared with the central-cuff method, but also indicate the need for further refinement of the cuff technique.

The reservoir-excess pressure model of arterial hemodynamics was first applied to invasive BP waveforms in animal models, and was conceived to circumvent conceptual limitations with wave only models of the arterial system.[2, 98, 99, 15] More importantly, the approach has been applied to clinical populations on BP waveforms captured non-invasively outside of the aorta (including the carotid and radial arteries) via tonometry, and consistently shown that reservoir pressure parameters (e.g. RP, XSP, systolic rate constant) have prognostic value beyond standard BP and other cardiovascular risk factors.[4-6, 24] The value of this current study is the demonstration that it is technically feasible to use a cuff-based method to derive reservoir pressure parameters. The cuff technique is user-friendly and non-operator dependent, thus should have improved ease of use (compared with tonometry or invasive methods) and has the possibility for assessment over 24 hours.[15] However, significant improvement in the estimation of reservoir pressure parameters using the cuff device is needed as waveform data from 18% of available participants were excluded due to the non-physiological P∞> diastolic BP (and

this was experienced under resting conditions, let alone whilst ambulatory where greater errors would be expected). Furthermore, from the available data, the rate constants of reservoir pressure parameters could not be accurately reproduced using the non-invasive cuff methods applied in this study. This is likely to have arisen from the recording of the brachial-cuff volumetric waveforms at sub-diastolic BP, which dampens waveform features, but is a problem that might be resolvable with waveform capture at higher inflation pressures.[86] Issues of systematic bias (figures 4 and 5) also need to be corrected so that the method has accuracy and applicability across a broad range of BP. Importantly, it is still yet to be determined if cuff-derived measurements of reservoir pressure parameters have clinical value in the assessment of cardiovascular risk compared to BP methods already available. Accordingly, the next steps will be to determine the independent association of cuff-derived reservoir pressure parameters with clinical indicators of arterial disease.

We expected good concordance between non-invasive cuff and intra-aortic RP because RP is relatively constant from central to peripheral human large arteries.[49, 100, 19] In fact, we observed moderate-to-good concordance of non-invasive cuff RP with intra-aortic RP (both brachial-cuff and central-cuff measurements, and both RP peak and RP integral assessments), but with cuff underestimation. A major factor likely contributing to this variation between non-invasive cuff and intra-aortic RP values is the volumetric technique related to measurement of the cuff BP waveform, rather than internal inconsistencies with the reservoir-excess pressure model itself. Volume displacement waveforms captured in the lower pressure range (10 mmHg lower than the diastolic BP) provide a relatively featureless signal by comparison to intra-aortic BP waveforms. The observed RP underestimation is also likely attributable to the calibration of brachial volumetric waveforms, which probably introduced an error of underestimated systolic BP, but overestimated diastolic BP.[101] Moreover, we found a trend towards greater underestimation of intra-aortic RP at higher RP values in both brachial-cuff and central-cuff

measurements. This trend might be related to greater underestimation of brachial systolic BP as systolic BP increases using the XCEL device,[102] which is common for oscillometric devices.[54, 55, 23]

On the other hand, compared with intra-aortic XSP, brachial-cuff XSP was higher, but central-cuff XSP was lower. The higher brachial-cuff XSP and lower central-cuff XSP are concordant with the findings of our recent invasive study that XSP is amplified in peripheral arteries compared with the aorta.[49, 100, 19] We think there are two major reasons for the brachial-cuff overestimation. Firstly, even though inaccurate calibration by cuff oscillometry (mentioned above) would reduce the overall amplitude of the brachial-cuff BP waveform compared with invasive BP waveform, maintenance of higher XSP values (both peak and integral) suggests that the shape of the systolic portion of the waveform was reasonably well maintained, as XSP is predominantly determined by wave travel in systole.[2] Secondly, we have previously demonstrated that XSP undergoes significant amplification from the aorta to the brachial (and radial) artery in parallel with the increase in systolic BP.[100] Therefore, even though the reference (invasive) brachial XSP would have been underestimated by the cuff waveform approach, it was reasonably concordant with the intra-aortic XSP because this variable is significantly lower than intra-brachial XSP. These observations may help to explain the strong associations between XSP derived from the radial artery and target organ damage,[4, 18, 19, 23] i.e. because this brachial-cuff approach is a reasonable estimate of the aortic XSP.

On the contrary, central-cuff XSP significantly underestimated the intra-aortic XSP, and trended towards greater underestimation with increasing XSP values. This is likely from inaccurate calibration of brachial-cuff BP waveforms and use of a GTF. Calibration with cuff oscillometry shrinks the amplitude of the brachial-cuff BP waveform, which imputes an underestimated magnitude of the true aortic BP waveform into the central-cuff BP

measurement. In fact, we found that central-cuff method underestimated intra-aortic systolic BP (-9±11 mmHg) and overestimated intra-aortic diastolic BP (9±7 mmHg). This result has been similarly reported by Shoji and colleagues[102], who found 5±10 mmHg central-cuff systolic BP underestimation and 13±6 mmHg central-cuff diastolic BP overestimation among 36 people.

Study strengths include the large sample size for an invasive study and employment of high grade standardized intra-arterial procedures designed to minimize potential sources of error.[103] However, study participants were undergoing diagnostic coronary angiography and most had at least one comorbidity or evidence of coronary artery disease, thus, results may not be generalizable to healthy populations. Secondly, even though we followed guideline best practice for intra-aortic BP waveform recordings, it would have been optimal to use solid state catheters rather than the fluid-filled catheter system. Another possible limitation was derivation of reservoir pressure parameters based on the pressure-only equation, which does not take into account variations in local blood flow. Nevertheless, the pressure-only approach demonstrates equivalence to the pressure-flow method.[39]

4.6 Conclusion.

We conclude that RP can be derived non-invasively from the brachial and central BP waveforms measured using the clinically convenient cuff device with reasonable concordance to intra-aortic measures, whereas XSP can only be acceptably derived from the brachial BP waveforms. There are some methodological considerations relating to the quality of BP waveform acquisition that limit the accuracy of non-invasive cuff measured reservoir pressure parameters by comparison to intra-aortic measures, and this is an area for future refinement of the method. The cuff-based approach to measuring reservoir pressure parameters is user-

friendly and operator-independent, which should enable more widespread application of brachial-cuff RP and XSP to determine the clinical significance of reservoir pressure.

4.7 Contribution of chapter 4 to thesis aims

Chapter 4 is the first study to determine if reservoir pressure parameters could be reliably estimated from a non-invasive, cuff BP measurement method. This was conducted by simultaneous comparison of non-invasive reservoir pressure parameters estimated from cuff-based measurement of brachial and central BP waveforms with invasive-aortic recordings among 162 people. When comparing the consistency between brachial-cuff and intra-aortic measurements, there was moderate-to-good consistency for RP, and poor-to-moderate consistency for XSP. When comparing the consistency between central-cuff and intra-aortic measurements, there was moderate-to-good consistency for RP, but poor consistency for XSP. These findings indicate that the brachial-cuff method more reliably estimates intra-aortic RP and XSP with acceptable consistency, although there is an area for future refinement, such as improving the accuracy of BP waveform measurement in diastole and reducing the error between cuff device measured BP and intra-aortic BP. Thus, chapter 5 seeks to determine whether brachial-cuff RP and XSP are clinically relevant to cardiovascular risk markers, and this will be investigated using data from a large population of Australian adults.

Chapter 5 – Association of brachial-cuff excess pressure with carotid intima-media thickness in Australian adults: a cross-sectional study

This thesis chapter is fully drafted and under co-authors' review.

Peng X, Schultz MG, Wake M, Mynard J, Cheung M, Otahal P, Burgner D, Ellul S, Liu R, Juonala M, Sharman JE

Presentations:

- Association for Research Arterial Structure and Physiology 17 congress oral presentation in the Young Investigator Competition Session, Pisa, Italy, June 2017
- International Society of Hypertension oral presentation, Beijing, China, September 2018.

5.1 Abstract

Objective. Reservoir pressure parameters (reservoir pressure [RP], excess pressure [XSP] and systolic rate constant) measured using tonometry predict cardiovascular events beyond conventional risk factors. However, the operator-dependency of tonometry impedes widespread use. An operator-independent cuff-based device can acceptably estimate the intra-aortic RP and XSP from brachial volumetric waveforms, but whether these estimates are clinically relevant to cardiovascular risk markers has not been investigated.

Methods. RP and XSP were derived from brachial volumetric waveforms measured using cuff oscillometry (SphygmoCor Xcel) in 1691 mid-life adults from the CheckPoint study (a population-based cross-sectional study nested in the Longitudinal Study of Australian Children). Carotid intima-media thickness (carotid IMT, n=1447) and carotid-femoral pulse wave velocity (PWV, n=1632) were measured as cardiovascular risk markers.

Results. There was a small but significant association between XSP and carotid IMT (β=0.76 μm, 95%CI, 0.25 to 1.26, p=0.004, partial R^2=0.7%) after adjusting for age, sex, body mass index, heart rate, smoking, diabetes, high-density lipoprotein cholesterol and mean arterial pressure. Neither XSP nor RP were independently related to PWV. However, mean arterial pressure was found to mediate an association between RP and PWV (path coefficient=1.64, 95% CI, 1.25 to 2.04; p<0.001). **Conclusion.** Cuff-based XSP is significantly associated with carotid IMT, independent from conventional cardiovascular risk factors. This indicates that XSP could have clinical relevance, but the small magnitude of association may suggest that the cuff-based method needs refinement to derive higher precision for measurement of reservoir pressure parameters.

5.2 Introduction.

Cardiovascular disease remains the largest cause of mortality worldwide, and high blood pressure (BP) is the leading risk factor.[9, 27, 104] Conventional BP is derived from the estimation of the peak (systolic BP), nadir (diastolic BP) and area (MAP, mean arterial pressure) of brachial arterial BP waveforms. Several theoretical constructs have been proposed to explain the physiology underlying the BP waveform.[33] One such explanation is the reservoir-excess pressure model, which proposes that the total BP waveform comprises a reservoir pressure (RP, determined by the systemic arterial compliance and peripheral resistance) and an excess pressure (XSP, related to the local wave propagation) component.[3] Several reservoir pressure parameters (i.e. RP, XSP and the systolic rate constant) have been shown to predict cardiovascular morbidity and mortality above and beyond conventional risk factors.[4-6, 20, 22, 24, 26] All of these studies measured reservoir pressure parameters using tonometry at carotid or radial arteries, but this technique is highly operator-dependent[47] and has not yet been adopted in clinical settings.

Oscillometric cuff devices are routinely used for BP assessment, and this may offer a user-friendly and operator-independent method to undertake more widespread measurement of reservoir pressure parameters. We recently compared reservoir pressure parameters derived non-invasively using a cuff device (from brachial volumetric waveforms) with aortic reservoir pressure parameters recorded invasively by catheter. This study found acceptable concordance of the cuff-based measures with intra-aortic measures of RP and XSP (mean differences were -8±4 mmHg/s and 1±2 mmHg/s, and intra-class correlation coefficients were 0.66, 95% confidence interval [CI] 0.57 to 0.73 and 0.60, 95% CI 0.49 to 0.68).[79] This implies that the cuff-based method to derive reservoir pressure could have clinical utility, however, this remains to be determined. Therefore, this study aimed to examine the independent associations

between brachial-cuff reservoir pressure parameters and cardiovascular risk markers, including carotid pre-atherosclerosis and aortic stiffness, in a large population of Australian adults. We hypothesised that brachial-cuff reservoir pressure parameters would be independently associated with cardiovascular risk markers.

5.3 Methods.

Study population. Participants were the adult guardians (usually mothers) who accompanied the children that were participants in the Child Health CheckPoint study (CheckPoint). CheckPoint was a cross-sectional comprehensive assessment of physical health and biomarkers within the Longitudinal Study of Australian Children (LSAC) birth cohort, conducted between LSAC's sixth and seventh waves. LSAC applied a two-stage sampling design. The first phase was random selection of ten percent of all Australian postcodes (stratified by state and urban/rural domicile). The second phase involved selection of children from the Medicare database. 8928 health infants at age 0-1 years in 2014 were recruited for LSAC birth cohort. The response rate was 57.2% for wave 1 in 2004, of whom 73.7% were retained for wave 6 in 2014.[105] Checkpoint participants were recruited from wave 6, of which 1874 children and one of the adult guardians attended for assessment. Details of the study population and health assessment protocols in CheckPoint study have been published.[106, 107] The study protocol was approved by the Royal Children's Hospital Melbourne Human Research Ethics Committee (33225D) and Australian Institute of Family Studies Ethics Committee. Participants gave written informed consent.

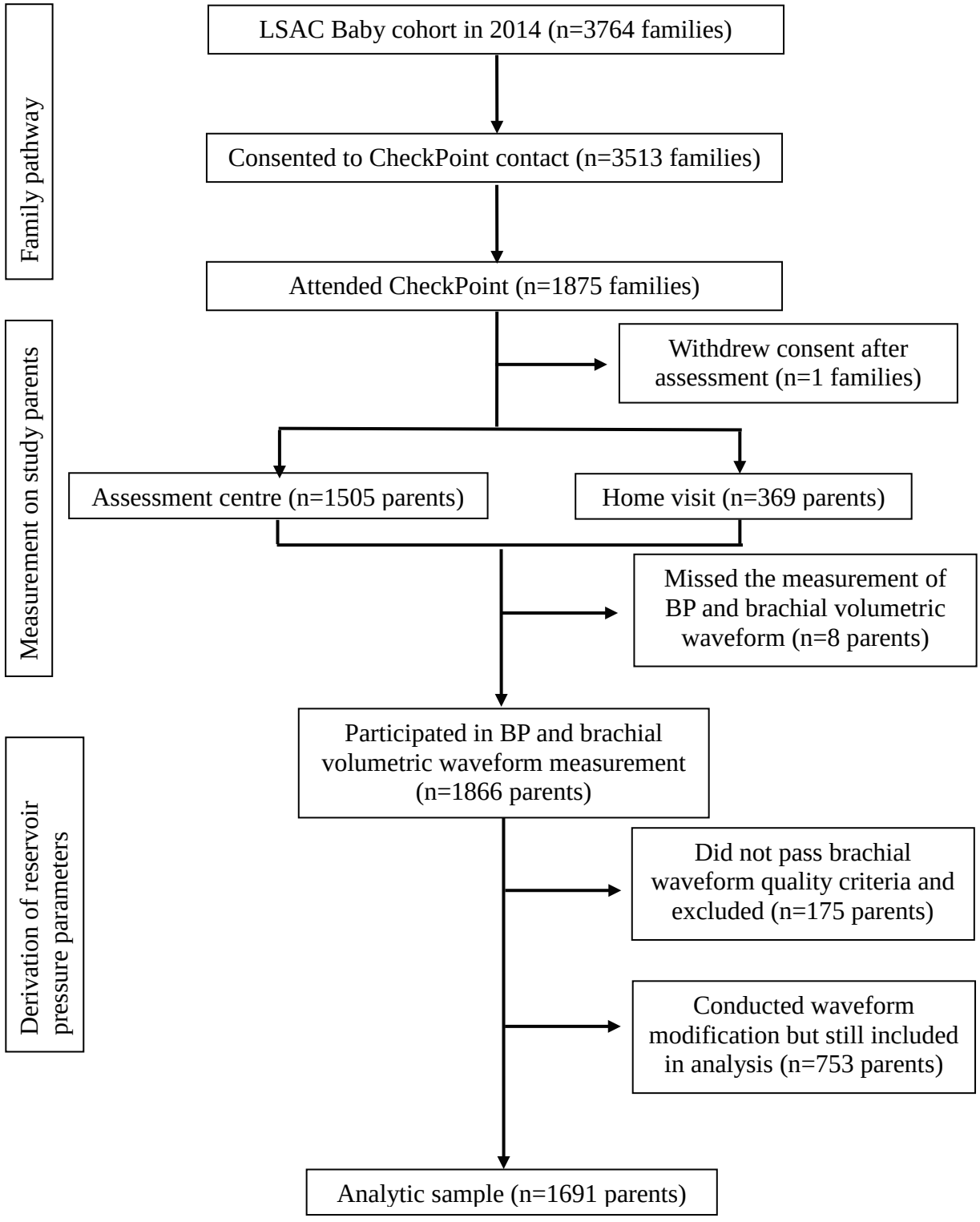


Figure 5.1 Summary of participant flow. One child and one of child's parents from LSAC families attended CheckPoint, but only parents' data were used in this study. Waveform modification refers to remove the additional small upslope after the nadir of the BP waveform in diastole.

Study procedures. The CheckPoint data collection spanned from February 2015 to March 2016. Participants preferentially attended one of 15 assessment centres nationwide (n=1509, 80%). If unable to attend, a shorter home visit was undertaken at the participant's home (n=365, 20%). Measurements of carotid intima-media thickness (carotid IMT) or lipids (i.e. total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides) were only obtained on participants who attended an assessment centre because these measurements were not feasible at home visits. All the other measures were obtained in both assessment centre and home visit settings.

Reservoir pressure parameters. Brachial BP and brachial volumetric waveforms were acquired in triplicate using an oscillometric cuff device (SphygmoCor Xcel, AtCor Medical Pty Ltd., West Ryde, Australia) in the supine position after seven minutes rest. Eight participants did not complete the measurement of brachial BP and brachial volumetric waveforms. Brachial volumetric waveforms were default ensemble averaged by the built-in software before calibration and consequent derivation of reservoir pressure parameters. A quality check of brachial BP waveforms was performed based on average pulse height (>80 units), pulse height variation (≤5%), diastolic variation (≤5%), shape deviation (≤4%), operator index (default evaluated and reported by SphymoCor Xcel, ≥75) and systolic BP between 50 and 200 mmHg. Only BP waveforms that passed all the quality criteria were eligible for inclusion and data from 175 participants were excluded. For each of the remaining 1691 participants, the first eligible brachial BP waveform was calibrated with the average of three brachial systolic and diastolic BPs.

Reservoir pressure parameters were calculated using a customised MATLAB program (Mathworks, Inc, Natick, MA) with the pressure-only approach as per equation 1.[6, 15]

$$\frac{dP_{reservoir}}{dt} = Sc(P - P_{reservoir}) - Dc(P_{reservoir} - P\infty)$$

Equation 5.1 Calculation of the reservoir pressure.

P is measured total pressure, $P_{reservoir}$ is RP, and $P_\infty$is the arterial asymptotic pressure. The systolic and diastolic rate constants (i.e. the rate constants relating to the speed of the upstroke and downstroke on the pressure waveform respectively) are *Sc* and *Dc*, where *a* = 1/ ZC and *b* = 1/RC (Z is a constant which will depend upon a number of factors, such as the local wave speed and cross-sectional area at the root of the aorta, C is the compliance of the whole arterial tree, and R is the effective resistance of the peripheral systemic circulation).[3] XSP is defined as the difference between the measured total pressure and RP. Figure 5.2 is an example BP waveform that shows the RP and XSP components. RP and XSP are expressed in both peak and integral, where the peak refers to the highest value and integral refers to the area under curve.

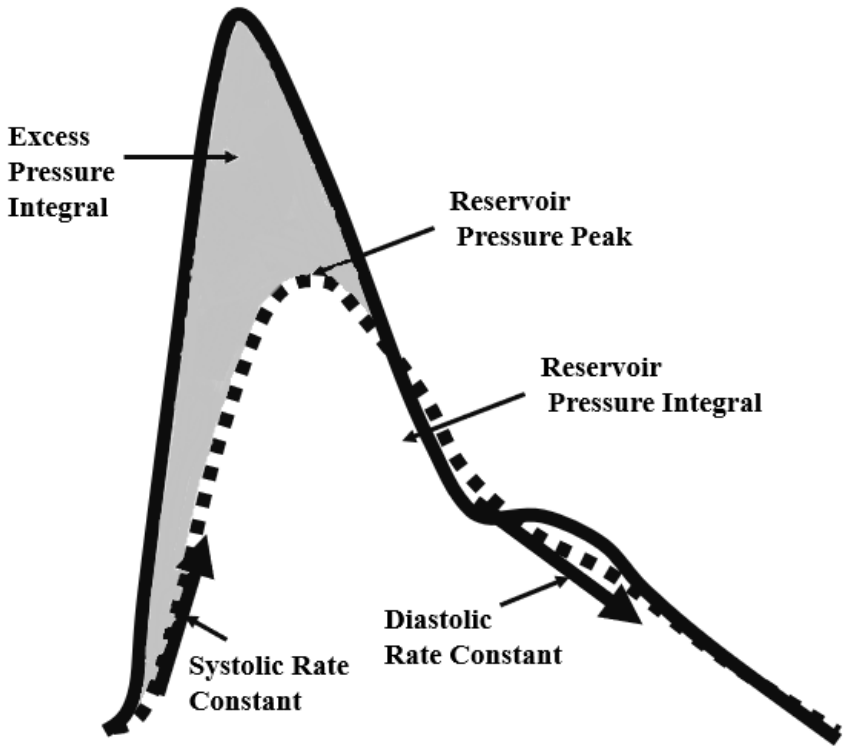


Figure 5.2 Blood pressure waveform (———) with example reservoir pressure parameters. The reservoir pressure (·····) and excess pressures (in shadow) are expressed as peak and integrals (area under the pressure curves).

The RP algorithm accommodates waveforms with exponential pressure decay during diastole but generates non-physiological values of P_∞ (i.e. that are greater than diastolic BP) in those with an additional small upslope after the nadir of the BP waveform in diastole. This problem appears to arise because the algorithm was applied to the ensemble averaged waveform without consideration of cardiac duration. Waveform modification was performed to resolve the problem, firstly by removal of the small upslope occurring at end diastole and then re-applying the algorithm to derive reservoir pressure parameters.

Cardiovascular risk markers. Carotid pre-atherosclerosis was determined by common carotid artery IMT using a high-performance ultrasound 10 MHz L-RS vascular probe (Vivid I Bt06, GE) in accordance with recommendations of the American Society of Echocardiography and Mannheim Consensus statements.[108] Images of the right common carotid artery were captured over 5-10 cardiac cycles (tracked using three-lead ECG) at 10 mm proximal to the carotid bulb in supine position. Ultrasonography was performed by six trained researchers. The inter- and intra-operator reliability of measurements was tested in 105 images. The within-observer coefficients of variation was 6.5% for mean carotid IMT values, and the between-observer coefficients of variation was 9.5%. Within-observer intra-class correlations were 0.71 (95% CI, 0.63–0.78), and between-observer intra-class correlations were 0.64 (95% CI, 0.54–0.74). B-mode ultrasound cine loops were captured in triplicate. The images were analysed using Carotid Analyzer (Medical Imaging Applications, Coralville, IA, USA) for semi-automated border detection, and this was blinded to reservoir pressure parameters value. The carotid IMT was measured as the mean thickness in millimetres of 3- to 5-frames of the one carotid IMT measurement over the 5- to 10-mm section. The average of three carotid IMT measurements was used in the analysis.

Aortic stiffness was measured by carotid-femoral pulse wave velocity (PWV) in triplicate according to the consensus guidelines[109] using SphygmoCor Xcel. A cuff was placed around the participant's upper thigh to capture the femoral artery pulse and a tonometer (Millar Micro-tip SPT-transducer, Houston, USA) was used to simultaneously record the carotid artery pulse. PWV was calculated as the distance between carotid and femoral recording sites divided by the pulse transit time. The distance was defined as the distance from sternal notch to top edge of femoral cuff minus the distance from carotid artery to sternal notch.

Other sample characteristics. Anthropometry was measured with the participants in light clothing and without shoes. Height was measured in duplicate using a portable stadiometer. If the difference between the two measurements was greater than 0.5 cm, a third measurement was taken. The mean of all measurements was used as height. Weight was measured using an InBody230 bio-electrical impedance analysis scale (Biospace Co. Ltd. Seoul, South Korea). Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2), and overweight was defined as BMI greater than 25 kg/m^2.[110] Lipids including total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides were measured in semi-fasting venous blood via the Nightingale® Nuclear Magnetic Resonance metabolomics platform.[111] Information on smoking and diabetes status were extracted from the self-reported questionnaire collected in LSAC wave 6, one year earlier. Smoking was defined based as consuming ≥1 cigarette per day. Diabetes was defined as either type 1 or type 2 diabetes. Heart rate was obtained during BP measurement using SphygmoCor Xcel. MAP was calculated as diastolic BP +1/3 (systolic BP – diastolic BP). Hypertension was defined according to BP ≥140/90 mmHg from the averaged triplicate BPs.

Statistical analysis. Continuous data were presented as mean (SD) and categorical data as %. 'Exposures' were RP peak, RP integral, XSP peak and XSP integral. 'Outcomes' were carotid

IMT and PWV. Uni- and multi-variable regression analyses were performed to examine the associations between exposures and outcomes. The units of carotid IMT and PWV were transformed to μm and cm/s respectively for presentation of data to appropriate significant figures. Conventional risk factors[112] were considered as potential covariates, and the risk factors that were correlated with both exposures and outcomes ($r>0.1$) or considered as physiologically important (i.e. heart rate), were included in the adjusted models. Altogether, sex, age, BMI, heart rate, smoking, diabetes and high-density lipoprotein cholesterol were included a priori in the basic-adjusted models, and further adjustment for each conventional BP measure (i.e. MAP, systolic BP, diastolic BP and pulse pressure) was included in the fully-adjusted models. Adjusting for each conventional BP had similar results, and thus results are only presented for MAP adjustment as the best representation of distending pressure.[61] Partial coefficients of determination (partial R^2) are presented as the percentage variance in outcomes explained by each risk factor. Interaction tests were performed to examine whether there was interaction between reservoir pressure parameters and sex in explaining cardiovascular risk markers, and no interaction was found. Thus, females and males were combined in analyses. Mediation analysis was performed to investigate whether the associations between exposures and outcomes were mediated indirectly through conventional BP. Data were analysed using Stata 1.5 (StataCorp LP, TX, USA).

5.4 Results.

Characteristics of the study population. Figure 5.1 shows the participant flow and table 1 presents the participant characteristics. The age of participants ranged from 28 to 71 and almost all were female. The prevalence of hypertension, smoking and diabetes were low, but the majority of participants (62%) were overweight.

Table 5.1 Characteristics of the study participants.

Variable	Mean (SD) or n (%)		
	All	Female	Male
n	1874	1644	230
Age (years)	44 (5)	44(5)	46 (7)
Sex (men %)	230 (11)		
Body mass index ($kg \cdot m^{-2}$)	28 (6)	28 (6)	28 (5)
Brachial systolic blood pressure (mmHg)	119 (13)	118 (13)	127 (12)
Brachial diastolic blood pressure (mmHg)	73 (9)	72 (9)	77 (8)
Hypertension (yes %)	164 (9)	123 (8)	41 (18)
Carotid intima-media thickness (μm)	568 (76)	561 (70)	610 (106)
Aortic pulse wave velocity (m/s)	6.9 (1.1)	6.8 (1.1)	7.5 (1.1)
Estimated glomerular filtration rate ($mL/min/1.73\ m^2$)	99 (12)	100 (12)	98 (12)
Heart rate (bpm)	64 (10)	64 (10)	63 (10)
RP peak (mmHg)	29 (8)	29 (9)	32 (9)
RP integral ($mmHg \cdot s^{-1}$)	11 (3)	11 (3)	12 (3)
XSP peak (mmHg)	27 (9)	26 (9)	28 (9)
XSP integral ($mmHg \cdot s^{-1}$)	5 (2)	5 (2)	5 (2)
Sc (s^{-1})	0.14 (0.08)	0.14 (0.09)	0.14 (0.08)
Dc (s^{-1})	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
Smoking (yes %)	203 (11)	185 (12)	18 (8)
Diabetes (yes %)	35 (2)	32 (2)	9 (4)
Lipid profile ($mmol \cdot L^{-1}$)			
High-density lipoprotein cholesterol	1.5 (0.4)	1.5 (0.4)	1.2 (0.3)
Low-density lipoprotein cholesterol	1.7 (0.4)	1.6 (0.4)	1.8 (0.4)
Triglycerides	1.5 (0.8)	1.4 (0.8)	2.0 (1.1)
Total cholesterol	4.8 (0.9)	4.8 (0.9)	4.9 (0.9)

n, number of subjects; RP, reservoir pressure; XSP, excess pressure; Sc, systolic rate constant; Dc, diastolic rate constant; Hypertension was defined based on systolic BP≥140 mmHg and/or diastolic BP≥ 90 mmHg of the averaged triplicate values measured at assessment centre, estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration.

Associations between reservoir pressure parameters and cardiovascular risk markers.

Carotid IMT. Table 5.2 summarises the associations between reservoir pressure parameters and carotid IMT in the uni- and multi-variable regression models. RP peak, RP integral, XSP peak and XSP integral were associated with carotid IMT in the univariable regression models. XSP peak and XSP integral remained as correlates of carotid IMT independent of age, sex, BMI, heart rate, smoking, diabetes and high-density lipoprotein cholesterol. However, the relationship was weak, only explaining less than 1% of the variance in carotid IMT, which was weaker than for age (≈5%) and male sex (≈3%), but stronger than MAP (0.5%). Furthermore, the direct association between XSP and carotid IMT substantially accounted for the total association (93.8 % for XSP peak, and 76.3% for XSP integral), and this was considerably stronger than the indirect association through MAP (6.2% for XSP peak, and 23.7% for XSP integral, model 3 and 4 in figure 5.3). RP peak and RP integral did not contribute additional meaningful variance in carotid IMT in the adjusted models.

PWV. Table 5.2 summarises the associations between reservoir pressure parameters and PWV in the uni- and multi-variable regression models. RP peak, RP integral, XSP peak and XSP integral were associated with PWV in univariable models. After adjusting for age, sex, BMI, heart rate, smoking, diabetes and high-density lipoprotein, RP continued to contribute to the total explainable variance in PWV. However, this was no longer meaningful after further adjusting for MAP, which indirectly but substantially influenced the pathway from RP to PWV as shown in model 5 and 6 in figure 5.3. The considerable effect of MAP on the association between RP and PWV was because of the stronger correlation between RP and MAP ($r=0.27$ for RP peak, and $r=0.33$ for RP integral, both $p<0.001$) and between MAP and PWV ($r=0.62$, $p<0.001$) than between RP and PWV ($r=0.11$ for RP peak, and $r=0.14$ for RP integral, both

$p<0.001$). However, XSP peak and XSP integral did not contribute meaningful variance in PWV in the multivariable models.

Table 5.2 Uni- and multi-variable regression models on the associations between reservoir pressure parameters and cardiovascular risk markers.

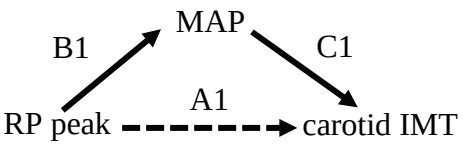
Model & predictor	Carotid IMT (μm)			Model & predictor	PWV (cm/s)		
	β (95% CI)	p	Partial R^2(%)		β (95% CI)	p	Partial R^2(%)
Univariable model	**n=1333**				**n=1333**		
RP peak (mmHg)	1.29 (0.85 to 1.72)	<0.001	0.2	RP peak (mmHg)	0.02 (0.01 to 0.02)	<0.001	1.2
RP integral (mmHg/s)	6.44 (4.18 to 8.70)	<0.001	0.7	RP integral (mmHg/s)	0.08 (0.05 to 0.10)	<0.001	2.1
XSP peak (mmHg)	1.28 (0.85 to 1.82)	<0.001	2.5	XSP peak (mmHg)	0.02 (0.02 to 0.03)	<0.001	3.8
XSP integral (mmHg/s)	6.44 (4.18 to 8.70)	<0.001	2.3	XSP integral (mmHg/s)	0.11 (0.08 to 0.14)	<0.001	2.6
Basic-adjusted model 1a	**n=1076**			**Basic-adjusted model 2a**	**n=1027**		
RP peak (mmHg)	0.29 (-0.24 to 0.81)	0.3	0.1	RP peak (mmHg)	0.01 (0.01 to 0.02)	0.005	0.8
RP integral (mmHg/s)	1.90 (-0.16 to 3.96)	0.07	0.3	RP integral (mmHg/s)	0.06 (0.03 to 0.09)	<0.001	1.5
XSP peak (mmHg)	0.80 (0.29 to 1.30)	0.002	0.9	XSP peak (mmHg)	0.01 (0.01 to 0.01)	0.2	0.2
XSP integral (mmHg/s)	3.82 (1.20 to 6.44)	0.004	0.8	XSP integral (mmHg/s)	0.02 (-0.01 to 0.06)	0.2	0.2
RP adjusted model 1b	**n=1067**			**RP adjusted model 2b**	**n=1021**		
Model R^2	0.17 (17%)			Model R^2	0.45 (45%)		
RP peak (mmHg)	0.09 (-0.46 to 0.65)	0.7	0.01	RP peak (mmHg)	-0.47 (-1.15 to 0.20)	0.2	0.2
MAP (mmHg)	0.69 (0.15 to 1.22)	0.01	0.5	MAP (mmHg)	5.80 (5.14 to 6.46)	<0.001	22.8
Age (years)	4.01 (3.14 to 4.88)	<0.001	6.5	Age (years)	4.20 (3.12 to 5.28)	<0.001	5.4
Male Sex	44.25 (30.06 to 58.44)	<0.001	3.0	Male Sex	24.28 (7.01 to 41.56)	0.006	0.8
Body mass index (kg/m^2)	0.68 (-0.21 to 1.58)	0.1	0.2	Body mass index (kg/m^2)	3.14 (1.99 to 4.29)	<0.001	2.8
Heart rate (bpm)	-0.41 (-0.94 to 0.13)	0.1	0.2	Heart rate (bpm)	0.03 (-0.62 to 0.69)	0.9	0.01
Smoking (yes)	6.89 (-7.02 to 20.81)	0.3	0.07	Smoking (yes)	-18.29 (-35.45 to -1.12)	0.04	0.4
Diabetes (yes)	28.73 (-0.80 to 58.25)	0.06	0.3	Diabetes (yes)	39.75 (2.00 to 77.49)	0.04	0.4
HDL (mmol/L)	-9.32 (-22.55 to 3.91)	0.2	0.2	HDL (mmol/L)	-13.93 (-30.00 to 2.13)	0.09	0.3
RP adjusted model 1c	**n=1067**			**RP adjusted model 2c**	**n=1021**		
Model R^2	0.17 (17%)			Model R^2	0.45 (45%)		
RP integral	1.03 (-1.23 to 3.29)	0.5	0.06	RP integral (mmHg/s)	-2.04 (-4.81 to 0.72)	0.2	0.2
MAP (mmHg)	0.62 (0.07 to 1.17)	0.03	0.4	MAP (mmHg)	5.85 (5.17 to 6.53)	<0.001	22.1

Model & predictor	Carotid IMT (μm)			Model & predictor	PWV (cm/s)		
	β (95% CI)	p	Partial R^2(%)		β (95% CI)	p	Partial R^2(%)
Age (years)	4.04 (3.18 to 4.90)	<0.001	6.7	Age (years)	4.25 (3.18 to 5.32)	<0.001	5.7
Male Sex	44.26 (30.13 to 58.39)	<0.001	3.0	Male Sex	23.53 (6.32 to 40.74)	0.007	0.7
Body mass index (kg/m^2)	0.67 (-0.22 to 1.56)	0.1	0.2	Body mass index (kg/m^2)	3.17 (2.02 to 4.32)	<0.001	2.8
Heart rate (bpm)	-0.35 (-0.90 to 0.20)	0.2	0.1	Heart rate (bpm)	-0.02 (-0.69 to 0.66)	0.9	0.01
Smoking (yes)	6.26 (-7.74 to 20.25)	0.4	0.06	Smoking (yes)	-17.42 (-34.68 to -0.16)	0.05	0.4
Diabetes (yes)	28.82 (-0.69 to 58.33)	0.06	0.3	Diabetes (yes)	39.33 (1.59 to 77.08)	0.04	0.4
HDL (mmol/L)	-9.40 (-22.63 to 3.83)	0.1	0.2	HDL (mmol/L)	-13.97 (-30.03 to 2.09)	0.09	0.3
XSP adjusted model 1b	**n=1067**			**XSP adjusted model 2b**	**n=1021**		
Model R^2	0.17 (17%)			Model R^2	0.45 (45%)		
XSP peak (mmHg)	0.76 (0.25 to 1.26)	0.004	0.7	XSP peak (mmHg)	0.04 (-0.59 to 0.67)	0.9	0.01
MAP (mmHg)	0.66 (0.15 to 1.17)	0.01	0.5	MAP (mmHg)	5.67 (5.03 to 6.30)	<0.001	23.3
Age (years)	3.70 (2.83 to 4.57)	<0.001	5.5	Age (years)	4.34 (3.25 to 5.43)	<0.001	5.7
Male Sex	45.06 (30.98 to 59.13)	<0.001	3.1	Male Sex	23.25 (6.02 to 40.47)	0.008	0.7
Body mass index (kg/m^2)	0.27 (-0.66 to 1.20)	0.6	0.03	Body mass index (kg/m^2)	3.13 (1.94 to 4.33)	<0.001	2.5
Heart rate (bpm)	-0.40 (-0.92 to 0.12)	0.2	0.2	Heart rate (bpm)	0.14 (-0.50 to 0.78)	0.7	0.02
Smoking (yes)	7.92 (-5.94 to 21.77)	0.3	0.1	Smoking (yes)	-18.87 (-36.04 to -1.70)	0.03	0.5
Diabetes (yes)	28.03 (-1.37 to 57.44)	0.06	0.3	Diabetes (yes)	39.66 (1.87 to 77.44)	0.04	0.4
HDL (mmol/L)	-8.66 (-21.84 to 4.53)	0.2	0.1	HDL (mmol/L)	-14.11 (-30.20 to 1.97)	0.09	0.3
XSP adjusted model 1c	**n=1067**			**XSP adjusted model 2c**	**n=1021**		
Model R^2	0.17 (17%)			Model R^2	0.45 (45%)		
XSP integral (mmHg/s)	3.69 (1.06 to 6.32)	0.006	0.6	XSP integral (mmHg/s)	0.95 (-2.31 to 4.20)	0.6	0.03
MAP (mmHg)	0.68 (0.17 to 1.19)	0.009	0.5	MAP (mmHg)	5.66 (5.03 to 6.30)	<0.001	23.3
Age (years)	3.62 (2.73 to 4.51)	<0.001	5.0	Age (years)	4.26 (3.15 to 5.37)	<0.001	5.3
Male Sex	46.62 (32.46 to 60.78)	<0.001	3.3	Male Sex	23.73 (6.42 to 41.04)	0.007	0.7
Body mass index (kg/m^2)	0.30 (-0.63 to 1.23)	0.5	0.03	Body mass index (kg/m^2)	3.06 (1.87 to 4.26)	<0.001	2.5

Model & predictor	Carotid IMT (μm)			Model & predictor	PWV (cm/s)		
	β (95% CI)	p	Partial R^2(%)		β (95% CI)	p	Partial R^2(%)
Heart rate (bpm)	-0.36 (-0.88 to 0.16)	0.2	0.2	Heart rate (bpm)	0.16 (-0.49 to 0.80)	0.6	0.02
Smoking (yes)	7.78 (-6.08 to 21.63)	0.3	0.09	Smoking (yes)	-18.75 (-35.92 to -1.59)	0.03	0.5
Diabetes (yes)	28.38 (-1.04 to 57.80)	0.06	0.3	Diabetes (yes)	39.60 (1.82 to 77.38)	0.04	0.4
HDL (mmol/L)	-8.77 (-21.96 to 4.42)	0.2	0.1	HDL (mmol/L)	-13.98 (-30.07 to 2.10)	0.09	0.3

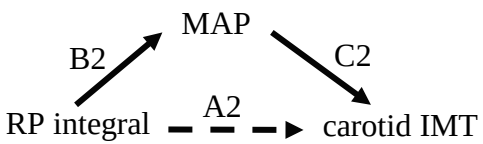
β refers to unstandardised beta coefficient as the μm difference in carotid intima-media thickness and the cm/s difference in carotid-femoral pulse wave velocity per unit increase in reservoir pressure parameters. CI, confidence interval. p value is for the unstandardised β. Model R^2 is the unadjusted model R^2 as a proportion 1. Partial R^2 (%) is the proportion of total variance in carotid intima-media thickness and in carotid-femoral pulse wave velocity explained by individual risk factor. Basic-adjusted models adjust for age, sex, BMI, heart rate, smoking, diabetes and high-density lipoprotein cholesterol. Fully-adjusted models have an additional mean arterial pressure above the basic-adjusted models. The series of model 1 is for carotid intima-media thickness, and the series of model 2 is for carotid-femoral pulse wave velocity. RP, reservoir pressure; XSP, excess pressure; HDL, high-density lipoprotein cholesterol; and, MAP, mean arterial pressure.

Model 1



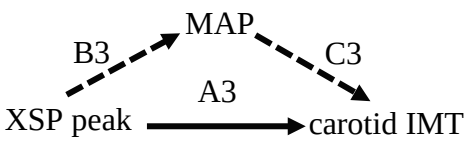
Path	Coefficient (95% CI)	p
A1	0.09 (-0.46 to 0.65)	0.7
B1C1	0.20 (0.01 to 0.37)	0.01

Model 2



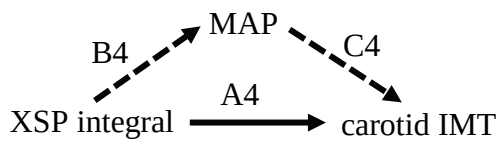
Path	Coefficient (95% CI)	p
A2	1.02 (-1.22 to 3.28)	0.4
B2C2	0.95 (0.09 to 1.80)	0.03

Model 3



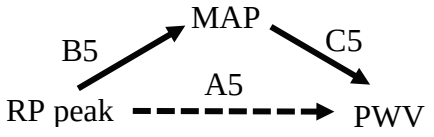
Path	Coefficient (95% CI)	p
A3	0.76 (0.25 to 1.26)	0.003
B3C3	0.05 (-0.01 to 0.10)	0.09

Model 4



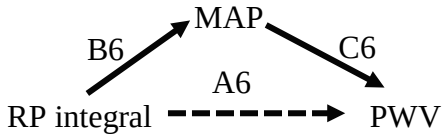
Path	Coefficient (95% CI)	p
A4	3.69 (1.08 to 6.30)	0.006
B4C4	1.15 (-0.09 to 0.39)	0.2

Model 5



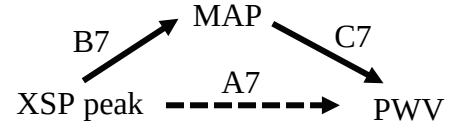
Path	Coefficient (95% CI)	p
A5	-0.47 (-1.14 to 0.20)	0.17
B5C5	1.64 (1.25 to 2.04)	<0.001

Model 6



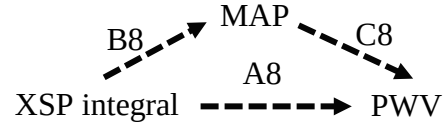
Path	Coefficient (95% CI)	p
A6	-2.04 (-4.80 to 0.71)	0.15
B6C6	8.64 (6.96 to 10.33)	<0.001

Model 7



Path	Coefficient (95% CI)	p
A7	0.04 (-0.59 to 0.67)	0.90
B7C7	0.44 (0.09 to 0.79)	0.01

Model 8



Path	Coefficient (95% CI)	p
A8	0.95 (-2.30 to 4.18)	0.57
B8C8	1.48 (-0.31 to 3.27)	0.11

Figure 5.3. Mediation analyses of the associations between reservoir pressure parameters and cardiovascular risk markers. Path models describe direct associations as well as indirect associations through mean arterial pressure. Effects are reported as standardised path coefficients along with the 95% confidence intervals (95% CI). p value is for the coefficient. Direct associations are labelled as path A, and indirect (mediating) associations are labelled as paths B–C. Solid arrows indicate significant association; broken arrows indicate non-significant association. Model 1-8 are adjusted for age, sex, body mass index, heart rate, smoking, diabetes and high-density lipoprotein cholesterol. XSP,

5.5 Discussion.

To our knowledge, this study is the first to apply a clinically convenient cuff approach to measure RP and XSP and investigate the associations with cardiovascular risk markers (carotid IMT and PWV) in a large population. The novel findings were that over and above conventional risk factors, XSP was associated with carotid IMT, and further that association between RP and PWV was mediated by MAP. These findings demonstrate in principle that brachial-cuff reservoir pressure parameters could provide useful information on cardiovascular risk in addition to traditional risk factors among adults, and thus might lead to better assessment of cardiovascular risk than current assessment strategies.

The above conclusions need to be taken in light of the relatively weak associations between reservoir pressure parameters and cardiovascular risk markers. This finding may have been influenced by a lack of precision in deriving reservoir pressure variables using the cuff-based technique employed in this study. This approach involved recording the brachial artery volumetric waveform at sub-diastolic (low) pressure, and then applying algorithms to derive reservoir pressure variables. Unfortunately, waveform features are dampened when recorded at low pressure, which means that some reservoir pressure variables cannot be accurately reproduced (e.g. the systolic and diastolic rate constants), and also probably leads to higher variance in derivation of XSP and RP.[79] Altogether, this indicates that refinement of the cuff-based method to derive higher precision for measurement of reservoir pressure parameters is probably needed before testing for potential clinical utility.

Having said this, the observed association between brachial-cuff XSP and carotid IMT was similar to that reported by the CAFÉ study investigators, who measured XSP integral at the radial artery using tonometry.[4] Although XSP is generally lower at the brachial artery than the radial artery,[100] the concordant findings suggest that the similar prognostic value of XSP for

predicting carotid IMT may be achievable at either measurement site.[4, 6] Our noteworthy new observation was that even though XSP marginally contributed to the total explainable variance in carotid IMT, this variable was ranked as the third strongest correlate of carotid IMT; only weaker than age and sex, and stronger than other traditional risk factors of BMI, smoking, diabetes, high-density lipoprotein cholesterol and MAP. However, the underlying physiological reasons to explain the association between brachial XSP and carotid IMT is unclear and requires further investigation.

Concordant to Davies et al.,[12] we found a positive association between RP and PWV, but also discovered that this association was mediated by MAP. The association between RP and PWV in the basic-adjusted models are plausible because there are overlapping arterial properties represented by both RP and PWV. RP is a systemic measure that is dependent on multiple factors, including left ventricular stroke volume, aortic diameter and stiffness, systemic arterial compliance and peripheral resistance,[3] whereas, PWV is a regional measure of arterial stiffness over a defined (central) arterial region.[109] The attenuation of the association between RP and PWV after inclusion of MAP in the multiple regression model may be driven by two factors. Firstly, greater than 70% proportion of MAP is attributable to RP integral[100], which leads to the strong correlation between MAP and RP. Secondly, distending pressure is a major determinant of PWV, and thus MAP strongly associates with PWV.[113, 114] Nevertheless, this study is an exploratory work and the mediating influence of MAP needs further confirmation.
The strength of this study includes a large nationally-derived population sample with a wide range of age and high-quality measures. The study also has wide social and geographic representation across Australia, but the sample is under-represented by families in a disadvantaged social-economic position,[107] and the results may not be generalizable to this population. Another potential limitation is that reservoir pressure parameters were measured in the supine position, whereas, clinical BP is usually measured whilst seated, and this could

influence findings. Furthermore, calculation of reservoir pressure parameters relied on a pressure-only approach (no flow), which involves additional assumptions.[115] Nevertheless, this method has been shown to produce substantially equivalent results to the pressure-flow method.[115]

5.6 Conclusion.

In conclusion, this study found that brachial-cuff reservoir pressure parameters were independently associated with cardiovascular risk markers separate from conventional cardiovascular risk factors among middle-age adults. The strength of the association between brachial-cuff XSP and carotid IMT was not very powerful and the full extent of clinical relevance is yet to be determined. Furthermore, brachial-cuff RP was related to PWV, but this association was mediated through conventional BP. Altogether, these findings suggest that a clinically convenient cuff approach to measuring reservoir pressure parameters may have potential clinical utility for better cardiovascular risk assessment, however, more investigations are required to confirm our observations.

5.7 Contribution of chapter 5 to thesis aims

Chapter 5 is the first study to apply brachial-cuff reservoir pressure parameters in a large population and investigate the potential clinical relevance. The principle findings were that brachial-cuff XSP was significantly associated with carotid sub-clinical atherosclerosis, RP was significantly related with arterial stiffness, and these were independent of conventional cardiovascular risk factors in adults. These results demonstrate that brachial-cuff reservoir pressure parameters could provide incremental information for the assessment of cardiovascular risk in addition to established risk factors among adults. Based on the convenient operation of the cuff device and the clinical relevance observed in chapter 5,

brachial-cuff reservoir pressure parameters may be applied more broadly to confirm the prognostic value for predicting cardiovascular events.

Chapter 6 – Conclusions and future directions.

This thesis is the first to confirm the changes in reservoir pressure parameters in central-to-upper limb, as well as the potential clinical feasibility and clinical importance of reservoir pressure parameters measured using a cuff technique. The thesis shows that the reservoir-excess model could be plausibly applied in the human upper arm (chapter 2); that a cuff device (SphygmoCor Xcel, Atcor) could reasonably estimate central BP (chapter 3); that the reservoir pressure parameters were more reliably estimated from the cuff-measured brachial BP waveforms than the cuff-measured central BP waveforms (chapter 4); and, finally, that brachial-cuff reservoir pressure parameters were significantly related to cardiovascular risk markers (chapter 5). Altogether, this thesis provides a novel understanding of the reservoir-excess pressure model and also provides evidence to help overcome the technical challenge of measuring non-invasive reservoir pressure parameters by the use of a clinically applicable cuff technique.

The physiology of reservoir pressure parameters along the large arteries of humans was invasively explored in chapter 2. The principal findings were that RP was unchanged and that XSP was amplified from the aorta to brachial and radial arteries. Although these findings are consistent with the understanding of reservoir-excess pressure model, the underlying mechanism of reservoir pressure parameters at different arterial sites is still unknown. The logical next steps will be undertaking more detailed exploration of the mechanisms of wave motion in the human large arteries. This exploration will require simultaneous pressure and flow measurements and wave-intensity analysis.

Furthermore, the different magnitudes of XSP along large arteries might affect the strength of associations between the XSP at different arterial sites and cardiovascular risk markers, which has never been investigated. Importantly, this future work should be conducted invasively to

get greater measurement precision than non-invasive techniques and provide in the veracity of the findings. Thus, the next step will be acquiring invasive reservoir pressure parameters at the aorta, brachial and radial arteries from participants undergoing coronary angiography and measuring cardiovascular risk markers (e.g., brain function, left ventricular structure, and kidney function). The strength of associations between the XSP at different arterial sites and cardiovascular risk markers should be assessed to identify the most clinically useful XSP along large arteries for predicting cardiovascular diseases and events.

Chapter 3 examined the performance of central BP measured using a cuff-based device by comparison to the radial tonometry method. The results showed substantial equivalence and good agreement between the cuff-estimated and tonometry-estimated central BP. Notwithstanding the good performance, the accuracy testing of the central BP estimation using the cuff device still needs to be strictly assessed in comparison to the intra-aortic standard measures according to the ARTERY Society guidelines and consensus.[103,116] In fact, there is one published work on the invasive validity of the Xcel device for estimating the central BP, but the sample size (n=36) did not meet the minimum number (n=85) proposed by expert consensus.[103] Thus, a logical next step will be testing the validity of the central BP estimated using the cuff device in comparison to intra-aortic measures in a population of at least 85 subjects.[103] Apart from the sample size, the "selection criteria, number of assessment phases, acceptable margin of error, BP range and pass/fail criteria"[103] should need to be thoroughly considered in order to obtain high-quality data.

The results of chapter 4 showed that it was feasible to derive RP and XSP with acceptable reliability using the non-invasive brachial-cuff method but that it was not possible to accurately estimate systolic and diastolic rate constants. The poor estimate of the rate constants indicates potentially missing features of the brachial-cuff BP waveform because the waveform was

captured at a sub-diastolic BP. This might be solvable by capturing at a supra-diastolic or even supra-systolic BP, which helps to preserve the features of arterial BP waveform, and this will be an area for future investigation. The improvement in the non-invasive method to estimate rate constants will need to be tested for validity against intra-arterial pressure waveforms – ideally using the micromanometer tipped catheters. Meanwhile, whether estimation accuracy of RP and XSP could be improved with the supra-diastolic or supra-systolic BP techniques could be assessed by comparison to intra-arterial measures.

The results of chapter 5 demonstrated the possible clinical relevance of brachial-cuff reservoir pressure parameters. The principal finding was that brachial-cuff RP and XSP were associated with cardiovascular risk markers, independent of conventional cardiovascular risk factors in a large population of Australian adults. Nevertheless, the strengths of the associations were not strong, and this could be due to the imperfect estimation of RP and XSP using the sub-diastolic cuff technique. If the estimation accuracy of RP and XSP could be improved with the refined technique (described above), the following step would be determining the associations of non-invasive reservoir pressure parameters measured using the refined technique with clinical outcomes in separate prospective population-based studies.

Furthermore, there were just two cardiovascular risk markers (i.e., the carotid IMT and aortic PWV) observed in chapter 5. To further confirm the clinical significance of reservoir pressure parameters, associations with more cardiovascular risk markers (e.g., left ventricular mass index and ratio of grey matter volume to white matter lesions) and with clinical cardiovascular events (e.g., stroke, heart attack, heart failure, and myocardial infarction) will need to be examined in future work. The data used in chapter 5 were from the LSAC study, which is an ongoing longitudinal study and will record the cardiovascular events that occur in the follow-

up period. This provides an opportunity for confirming the potential value of reservoir pressure parameters for predicting cardiovascular events.

Other future studies should aim to investigate reservoir pressure parameters in children and the heritability of reservoir pressure parameters between generations. It is noteworthy that reservoir pressure parameters have never been investigated in children, although reservoir pressure parameters might provide useful information for early interventions to prevent cardiovascular diseases in children's late life. Furthermore, a recently published study has shown that arterial properties are heritable. Specifically, the heritability between generations is 25% for the brachial artery diameter, 29% for the carotid IMT, 55% for the lumen diameter, and 26% for the aortic PWV.[117] These heritable properties may be useful for better prediction of CVD among children. The reservoir-excess model represents the properties of arterial haemodynamics, but the heritable variance of reservoir pressure parameters has not been investigated. LSAC has data from both parents' and children's reservoir pressure parameters, dietary habit and intensity of physical activity, and participants' socio-economic status and cultural environment. This should enable further heritability studies by assessing the heritable variance of reservoir pressure parameters between parents and children after adjusting for other potential covariables (e.g., the intensity of physical activity, socioeconomic status and level of education). These future studies in the area of paediatrics and genetics would provide information for the early prevention of CVD.

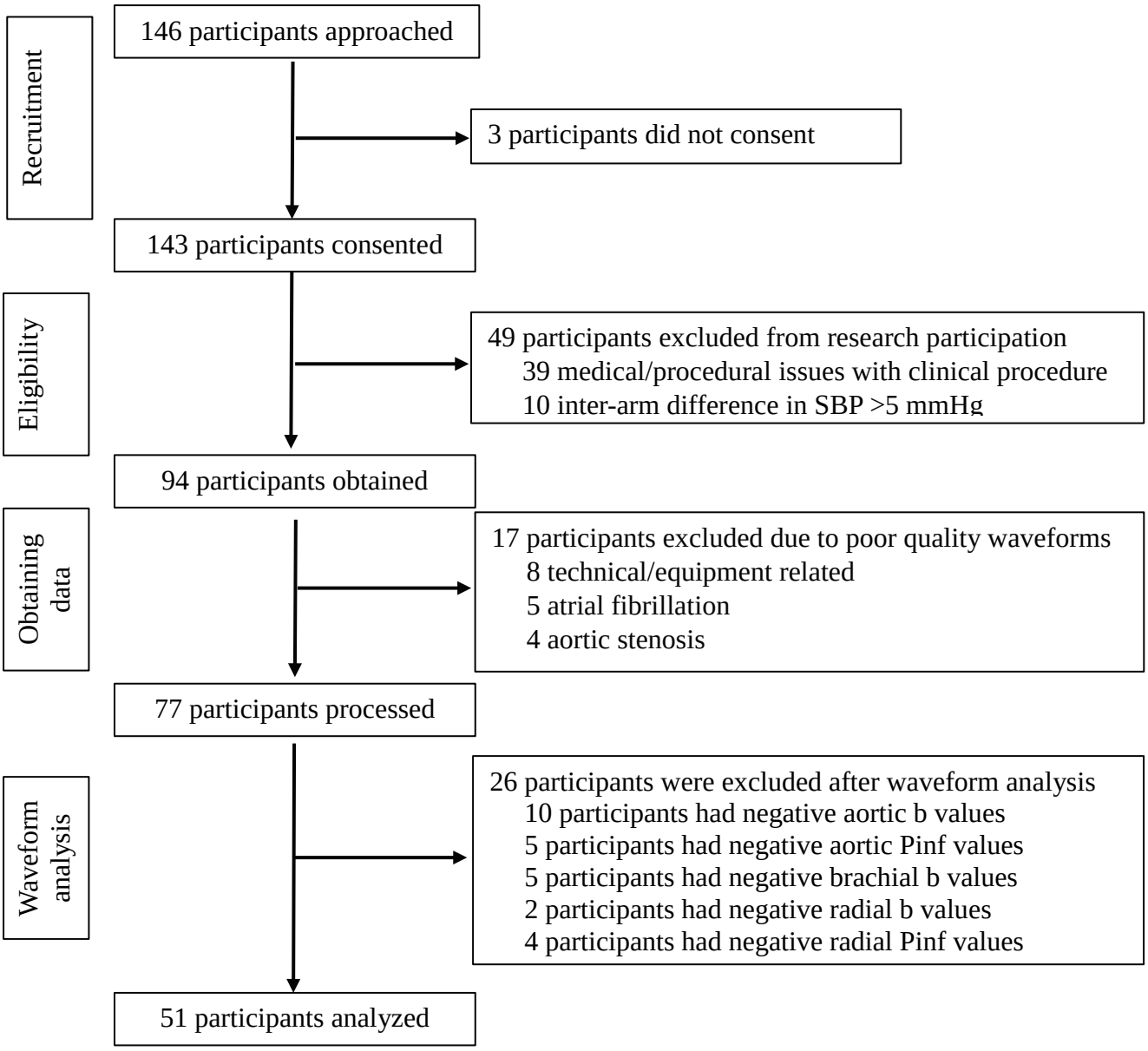
In summary, this thesis provides novel information that increases the understanding of reservoir-excess pressure model in humans, and an operator-independent and non-invasive cuff approach to measure reservoir pressure parameters. Moreover, these cuff reservoir pressure parameters are clinically relevant to cardiovascular risk markers. Future studies should aim to improve the measurement accuracy of reservoir pressure parameters, further confirm the

clinical importance of brachial-cuff reservoir pressure parameters for stratifying cardiovascular risk and expand the potential clinical implication of reservoir pressure parameters in children. Taken together, the easy-to-operate cuff approach may into the future may into the future facilitate wider application of reservoir pressure parameters for improving cardiovascular risk stratification and ultimately leading to better cardiovascular outcomes.

Appendices

Appendix 1

Supplementary material for chapter 2



Appendix Figure 1.1 Study flow diagram of participants. SBP, systolic blood pressure; b, diastolic rate constant; Pinf, pressure level.

Appendix Table 1.1 Age associates with central-to-peripheral change in reservoir pressure parameters.

	Aortic-Brachial Change	Brachial-Radial Change	Aortic-Radial Change
RP integral ($Pa \cdot s^{-1}$)	-0.036	-0.084	-0.105
RP peak (mmHg)	-0.037	0.031	<0.001
XSP integral ($Pa \cdot s^{-1}$)	-0.108	0.058	-0.037
XSP peak (mmHg)	-0.231	0.167	-0.041
Proportion RP (%)	0.093	-0.083	0.007
Proportion XSP (%)	-0.093	0.083	-0.007
XSP:RP (ratio)	-0.029	0.072	0.031
Systolic rate constant (s^{-1})	0.140	-0.120	0.012
Diastolic rate constant (s^{-1})	0.204	-0.132	0.060

Data are Pearson correlation co-efficient (r). No correlations were significant ($p<0.05$). RP, reservoir pressure; XSP, excess pressure; Proportion RP, the percentage contribution of RP to total pressure; Proportion XSP, the percentage contribution of XSP to total pressure; XSP: RP, the ratio of XSP contribution to RP contribution in the total pressure.

Bibliography.

1. Collaboration PS. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet*. 2002;360(9349):1903-1913.

2. Collaboration NCDRF. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet*. 2017;389(10064):37-55.

3. Wang JJ, O'Brien AB, Shrive NG, et al. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. *Am J Physiol Heart Circ Physiol*. 2003;284(4):H1358-68.

4. Davies JE, Lacy P, Tillin T, et al. Excess pressure integral predicts cardiovascular events independent of other risk factors in the conduit artery functional evaluation substudy of Anglo-Scandinavian Cardiac Outcomes Trial. *Hypertens*. 2014;64(1):60-8.

5. Hametner B, Wassertheurer S, Hughes AD, et al. Reservoir and excess pressures predict cardiovascular events in high-risk patients. *Int J Cardiol*. 2014;171(1):31-6.

6. Cheng HM, Chuang SY, Wang JJ, et al. Prognostic significance of mechanical biomarkers derived from pulse wave analysis for predicting long-term cardiovascular mortality in two population-based cohorts. *Int J Cardiol*. 2016;215:388-95.

7. Roth GA, Johnson C, Abajobir A, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70(1):1-25.

8. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2224-60.

9. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-13.

10. Sharman JE, Davies JE, Jenkins C, et al. Augmentation index, left ventricular contractility, and wave reflection. *Hypertens*. 2009;54(5):1099-105.

11. Vermeersch S, Rietzschel E, De Buyzere M, et al. The reservoir pressure concept: the 3-element windkessel model revisited? Application to the Asklepios population study. *J Eng Math*. 2009;64(4):417-428.

12. Davies JE, Baksi J, Francis DP, et al. The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. *American Journal of Physiology-Heart and Circulatory Physiology*. 2010;298(2):H580-H586.

13. Bia D, Cymberknop L, Zocalo Y, et al. Age-related changes in reservoir and excess components of central aortic pressure in asymptomatic adults. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:6454-7.

14. Cymberknop L, Bia D, Zocalo Y, et al. Gender-related differences in the excess pressure component of central aortic pressure waveform of healthy young. *Conf Proc IEEE Eng Med Biol Soc*. 2011;2011:207-10.

15. Heffernan KS, Yoon ES, Sharman JE, et al. Resistance exercise training reduces arterial reservoir pressure in older adults with prehypertension and hypertension. *Hypertens Res*. 2013;36(5):422-7.

16. Piskorski J, Krauze T, Katulska K, et al. Contribution of arterial excess pressure and arterial stiffness to central augmentation pressure in healthy subjects. *Int J Cardiol*. 2013;168(3):2899-900.

17. Schultz MG, Davies JE, Roberts-Thomson P, et al. Exercise central (aortic) blood pressure is predominantly driven by forward traveling waves, not wave reflection. *Hypertens*. 2013;62(1):175-182.

18. Climie RE, Srikanth V, Beare R, et al. Aortic reservoir characteristics and brain structure in people with type 2 diabetes mellitus; a cross sectional study. *Cardiovasc Diabetol*. 2014;13:143-152.

19. Climie RE, Srikanth V, Keith LJ, et al. Exercise excess pressure and exercise-induced albuminuria in patients with type 2 diabetes mellitus. *Am J Physiol Heart Circ Physiol*. 2015;308(9):H1136-42.

20. Narayan O, Davies JE, Hughes AD, et al. Central aortic reservoir-wave analysis improves prediction of cardiovascular events in elderly hypertensives. *Hypertens*. 2015;65(3):629-35.

21. Schultz MG, Hughes AD, Davies JE, et al. Associations and clinical relevance of aortic-brachial artery stiffness mismatch, aortic reservoir function, and central pressure augmentation. *Am J Physiol Heart Circ Physiol*. 2015;309(7):H1225-33.

22. Parragh S, Hametner B, Mayer C, et al. U-shaped relationship of reservoir pressure to cardiovascular events in patients with heart failure with reduced ejection fraction. *Artery Res*. 2016;16:55.

23. Climie RED, Picone DS and Sharman JE. Longitudinal Changes in Excess Pressure Independently Predict Declining Renal Function Among Healthy Individuals-A Pilot Study. *American Journal of Hypertension*. 2017;30(8):772-775.

24. Wang WT, Sung SH, Wang JJ, et al. Excess Pressure Integral Predicts Long-Term All-Cause Mortality in Stable Heart Failure Patients. *Am J Hypertens*. 2017;30(3):271-278.

25. Wohlfahrt P, Melenovsky V, Redfield MM, et al. Aortic Waveform Analysis to Individualize Treatment in Heart Failure. *Circ Heart Fail*. 2017;10(2):e003516.

26. Schneider A, Krauze T, Minczykowski A, et al. Arterial excessreservoir pressure integral as a predictor of cardiovascular complications in patients with acute coronary syndrome. *Pol Arch Intern Med*. 2018;128(4):228-234.

27. Collaborators GBDRF. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1659-1724.

28. O'rourke MF, Pauca A and Jiang XJ. Pulse wave analysis. *British journal of clinical pharmacology*. 2001;51(6):507-522.

29. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertens*, 2018, 71.6: E136-E139.

30. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-72.

31. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood pressure*. 2013;22(4):193-278.

32. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387(10022):957-67.

33. Segers P, O'Rourke MF, Parker K, et al. Towards a consensus on the understanding and analysis of the pulse waveform: Results from the 2016 Workshop on Arterial Hemodynamics: Past, present and future. *Artery Res*. 2017;18:75-80.

34. Sharman JE and Laurent S. Central blood pressure in the management of hypertension: soon reaching the goal? *J Hum Hypertens*. 2013;27(7):405-11.

35. Eather KF, Peterson LH and Dripps RD. Studies of the circulation of anesthetized patients by a new method for recording arterial pressure and pressure pulse contours. *Anesthesiology: The Journal of the American Society of Anesthesiologists*. 1949;10(2):195-195.

36. Frank O. Die grundform des arteriellen pulses. *Z Biol*. 1899;37(483-526):459.

37. Westerhof N, Sipkema P, van den Bos GC, et al. Forward and backward waves in the arterial system. *Cardiovasc Res*. 1972;6(6):648-56.

38. Parker KH and Jones C. Forward and backward running waves in the arteries: analysis using the method of characteristics. *J Biomech Eng*. 1990;112(3):322-326.

39. Davies JE, Hadjiloizou N, Leibovich D, et al. Importance of the aortic reservoir in determining the shape of the arterial pressure waveform–the forgotten lessons of Frank. *Artery Res*. 2007;1(2):40-45.

40. Parker KH, Alastruey J and Stan GB. Arterial reservoir-excess pressure and ventricular work. *Med Biol Eng Comput*. 2012;50(4):419-24.

41. Schultz MG, Davies JE, Hardikar A, et al. Aortic reservoir pressure corresponds to cyclic changes in aortic volume: physiological validation in humans. *Arteriosclerosis, thrombosis, and vascular biology*. 2014;34(7):1597-603.

42. Tyberg JV, Shrive NG, Bouwmeester JC, et al. The reservoir-wave paradigm: potential implications for hypertension. *Current Hypertension Reviews*. 2008;4(3):203-213.

43. Climie R, Otahal P, Schultz M, et al. A systematic review and meta-analysis of central to brachial blood pressure amplification in patients type 2 diabetes mellitus. *Artery Res*. 2015;12:45.

44. Hametner B and Wassertheurer S. Pulse Waveform Analysis: Is It Ready for Prime Time? *Curr Hypertens Rep*. 2017;19(9):73.

45. O'Rourke MF and Adji A. Central pressure and pulse wave amplification in the upper limb. *Hypertens*. 2010;55(1):e1-2; author reply e3.

46. Reymond P, Westerhof N and Stergiopulos N. Systolic hypertension mechanisms: effect of global and local proximal aorta stiffening on pulse pressure. *Annals of biomedical engineering*. 2012;40:742-749.

47. McEniery CM, Cockcroft JR, Roman MJ, et al. Central blood pressure: current evidence and clinical importance. *Eur Heart J*. 2014;35(26):1719-25.

48. Aguado-Sierra J, Alastruey J, Wang J, et al. Separation of the reservoir and wave pressure and velocity from measurements at an arbitrary location in arteries. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine*. 2008;222(4):403-416.

49. Narayan O, Parker KH, Davies JE, et al. Reservoir pressure analysis of aortic blood pressure: an in-vivo study at five locations in humans. *J Hypertens*. 2017;35(10):2025-2033.

50. Wang J, Jr., Bouwmeester JC, Belenkie I, et al. Alterations in aortic wave reflection with vasodilation and vasoconstriction in anaesthetized dogs. *Canadian Journal of Cardiology*. 2013;29(2):243-253.

51. Wang J, Jr., Shrive NG, Parker KH, et al. Wave propagation and reflection in the canine aorta: analysis using a reservoir-wave approach. *Canadian Journal of Cardiology*. 2011;27(3):389. e1-389. e10.

52. MacKay RS, Marg E and Oechsli R. Automatic tonometer with exact theory: various biological applications. *Science*. 1960;131(3414):1668-1669.

53. Kelly R, Hayward C, Winter D, et al. Non-invasive registration of the arterial-pressure pulse waveform using high-fidelity applanation tonometry. *Australian and New Zealand Journal of Medicine*. 1988;18:374-374.

54. Omboni S, Parati G, Groppelli A, et al. Performance of the AM-5600 blood pressure monitor: comparison with ambulatory intra-arterial pressure. *Journal of applied physiology*. 1997;82(2):698-703.

55. Groppelli A, Omboni S, Parati G, et al. Evaluation of noninvasive blood pressure monitoring devices Spacelabs 90202 and 90207 versus resting and ambulatory 24-hour intra-arterial blood pressure. *Hypertens*. 1992;20(2):227-32.

56. Butlin M, Qasem A and Avolio AP. Estimation of central aortic pressure waveform features derived from the brachial cuff volume displacement waveform. *Conf Proc IEEE Eng Med Biol Soc*. 2012;2012:2591-4.

57. Instrumentation AftAoM. American National Standard Non-invasive sphygmomanometers–part 2: Clinical validation of automated measurement type ISO 81060-2/ANSI-AAMI. 2013.

58. Kollias A, Lagou S, Zeniodi ME, et al. Association of Central Versus Brachial Blood Pressure With Target-Organ Damage: Systematic Review and Meta-Analysis. *Hypertens*. 2016;67(1):183-90.

59. Pauca AL, O'Rourke MF and Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertens*. 2001;38(4):932-7.

60. Sharman J, Stowasser M, Fassett R, et al. Central blood pressure measurement may improve risk stratification. *Journal of human hypertension*. 2008;22(12):838-844.

61. Nichols W, O'Rourke M and Vlachopoulos C. McDonald's blood flow in arteries: theoretical, experimental and clinical principles: CRC Press; 2011.

62. Tyberg JV, Bouwmeester JC, Parker KH, et al. The case for the reservoir-wave approach. *Int J Cardiol*. 2014;172(2):299-306.

63. Narayan O, Davies J, Hughes AD, et al. 7C.03: RESERVOIR PRESSURE ANALYSIS APPLIED AT FIVE LOCATIONS IN THE HUMAN AORTA. *J Hypertens*. 2015;33 Suppl 1:e96-7.

64. Hawkes N. Sixty seconds on . . . measuring blood pressure. *BMJ*. 2016;353:i2626.

65. Gardner RM. Direct blood pressure measurement--dynamic response requirements. *Anesthesiology*. 1981;54(3):227-36.

66. Costello BT, Schultz MG, Black JA, et al. Evaluation of a brachial cuff and suprasystolic waveform algorithm method to noninvasively derive central blood pressure. *Am J Hypertens*. 2015;28(4):480-6.

67. Millasseau SC, Patel SJ, Redwood SR, et al. Pressure wave reflection assessed from the peripheral pulse: is a transfer function necessary? *Hypertens*. 2003;41(5):1016-20.

68. Davies JE, Baksi J, Francis DP, et al. The arterial reservoir pressure increases with aging and is the major determinant of the aortic augmentation index. *Am J Physiol Heart Circ Physiol*. 2009;298(2):H580-6.

69. McEniery CM, Yasmin, Hall IR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol*. 2005;46(9):1753-60.

70. Schultz MG, Hughes AD, Davies JE, et al. Associations and clinical relevance of aortic-brachial artery stiffness mismatch, aortic reservoir function and central pressure augmentation. *Am J Physiol Heart Circ Physiol*. 2015:ajpheart 00317 2015.

71. Davies JE, Hadjiloizou N, Leibovich D, et al. Importance of the aortic reservoir in determining the shape of the arterial pressure waveform – The forgotten lessons of Frank. *Artery Res*. 2007;1(2):40-45.

72. Westerhof BE, van den Wijngaard JP, Murgo JP, et al. Location of a reflection site is elusive: consequences for the calculation of aortic pulse wave velocity. *Hypertension*. 2008;52(3):478-83.

73. Hope SA, Tay DB, Meredith IT, et al. Waveform dispersion, not reflection, may be the major determinant of aortic pressure wave morphology. *Am J Physiol Heart Circ Physiol*. 2005;289(6):H2497-502.

74. Davies JE, Alastruey J, Francis DP, et al. Attenuation of wave reflection by wave entrapment creates a "horizon effect" in the human aorta. *Hypertens*. 2012;60(3):778-85.

75. Zambanini A, Cunningham SL, Parker KH, et al. Wave-energy patterns in carotid, brachial, and radial arteries: a noninvasive approach using wave-intensity analysis. *Am J Physiol Heart Circ Physiol*. 2005;289(1):H270-6.

76. Khir AW and Parker KH. Wave intensity in the ascending aorta: effects of arterial occlusion. *J Biomech*. 2005;38(4):647-55.

77. Baksi AJ, Davies JE, Hadjiloizou N, et al. Attenuation of reflected waves in man during retrograde propagation from femoral artery to proximal aorta. *Int J Cardiol*. 2016;202:441-5.

78. Aguado-Sierra J, Hadjilizou N, Davies JE, et al. Pressure reservoir-wave separation applied to the coronary arterial data. *Conf Proc IEEE Eng Med Biol Soc*. 2007;2007:2693-6.

79. Peng X, Schultz MG, Picone DS, et al. Non-invasive measurement of reservoir pressure parameters from brachial-cuff blood pressure waveforms. *J Clin Hypertens (Greenwich)*. 2018;20(12):1703-1711.

80. Pini R, Cavallini MC, Palmieri V, et al. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARe Dicomano Study. *J Am Coll Cardiol*. 2008;51(25):2432-9.

81. Roman MJ, Devereux RB, Kizer JR, et al. High central pulse pressure is independently associated with adverse cardiovascular outcome: the Strong Heart Study. *Journal of the American College of Cardiology*. 2009;54(18):1730-1734.

82. Sharman JE, Marwick TH, Gilroy D, et al. Randomized trial of guiding hypertension management using central aortic blood pressure compared with best-practice care: principal findings of the BP GUIDE study. *Hypertension*. 2013;62(6):1138-45.

83. Vlachopoulos C, Aznaouridis K, O'Rourke MF, et al. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J*. 2010;31(15):1865-71.

84. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European heart journal*. 2013;34(28):2159-219.

85. Chen CH, Nevo E, Fetics B, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Validation of generalized transfer function. *Circulation*. 1997;95(7):1827-36.

86. Millasseau S and Agnoletti D. Non-invasive estimation of aortic blood pressures: A close look at current devices and methods. *Current pharmaceutical design*. 2015;21(6):709-718.

87. Mahieu D, Kips J, Rietzschel ER, et al. Noninvasive assessment of central and peripheral arterial pressure (waveforms): implications of calibration methods. *J Hypertens*. 2010;28(2):300-5.

88. Bos WJ, Verrij E, Vincent HH, et al. How to assess mean blood pressure properly at the brachial artery level. *J Hypertens*. 2007;25(4):751-755.

89. Wassertheurer S and Baumann M. Assessment of systolic aortic pressure and its association to all cause mortality critically depends on waveform calibration. *Journal of hypertension*. 2015;33(9):1884-1889.

90. Protogerou AD, Argyris AA, Papaioannou TG, et al. Left-ventricular hypertrophy is associated better with 24-h aortic pressure than 24-h brachial pressure in hypertensive patients: the SAFAR study. *Journal of hypertension*. 2014;32(9):1805-1814.

91. Weber T, Wassertheurer S, Rammer M, et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. *Hypertension*. 2011;58(5):825-832.

92. Meidert AS, Huber W, Hapfelmeier A, et al. Evaluation of the radial artery applanation tonometry technology for continuous noninvasive blood pressure monitoring compared with central aortic blood pressure measurements in patients with multiple organ dysfunction syndrome. *Journal of critical care*. 2013;28(6):908-912.

93. Picone DS, Climie RE, Ahuja KD, et al. Brachial-to-radial SBP amplification: implications of age and estimated central blood pressure from radial tonometry. *J Hypertens*. 2015;33(9):1876-83; discussion 1883.

94. Agnoletti D, Millasseau S, Topouchian J, et al. Pressure wave shape comparison between two non-invasive tonometric devices. *Annales de cardiologie et d'angeiologie*. 2013;62:193-199.

95. Jones SC, Bilous M, Winship S, et al. Validation of the OSCAR 2 oscillometric 24-hour ambulatory blood pressure monitor according to the International Protocol for the validation of blood pressure measuring devices. *Blood pressure monitoring*. 2004;9(4):219-223.

96. Goodwin J, Bilous M, Winship S, et al. Validation of the Oscar 2 oscillometric 24-h ambulatory blood pressure monitor according to the British Hypertension Society protocol. *Blood pressure monitoring*. 2007;12(2):113-117.

97. Koo TK and Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *Journal of chiropractic medicine*. 2016;15(2):155-163.

98. Tyberg JV, Bouwmeester JC, Shrive NG, et al. CrossTalk opposing view: Forward and backward pressure waves in the arterial system do not represent reality. *The Journal of physiology*. 2013;591(5):1171-1173.

99. Tyberg JV, Davies JE, Wang Z, et al. Wave intensity analysis and the development of the reservoir-wave approach. *Med Biol Eng Comput*. 2009;47(2):221-32.

100. Peng X, Schultz MG, Picone DS, et al. Arterial reservoir characteristics and central-to-peripheral blood pressure amplification in the human upper limb. *J Hypertens*. 2017;35(9):1825-1831.

101. Picone DS, Schultz MG, Otahal P, et al. Accuracy of Cuff-Measured Blood Pressure: Systematic Reviews and Meta-Analyses. *J Am Coll Cardiol*. 2017;70(5):572-586.

102. Shoji T, Nakagomi A, Okada S, et al. Invasive validation of a novel brachial cuff-based oscillometric device (SphygmoCor XCEL) for measuring central blood pressure. *J Hypertens*. 2017;35(1):69-75.

103. Sharman JE, Avolio AP, Baulmann J, et al. Validation of non-invasive central blood pressure devices: ARTERY Society task force consensus statement on protocol standardization. *Eur Heart J*. 2017;38(37):2805-2812.

104. Kannel WB. Role of blood pressure in cardiovascular disease: The Framingham Study. *Angiology*. 1975;26(1):1-14.

105. Norton A and Monahan K. Wave 6 weighting and non-response. *LSAC technical paper*. 2015;15.

106. Wake M, Clifford S, York E, et al. Introducing Growing Up in Australia's Child Health CheckPoint.

107. Services DoS. Longitudinal Study of Australian Children Release 7.0 (Waves 1-7), Additional Files. 2018.

108. Stein JH, Korcarz CE, Hurst RT, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force endorsed by the Society for Vascular Medicine. *Journal of the American Society of Echocardiography*. 2008;21(2):93-111.

109. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens*. 2012;30(3):445-448.

110. Organization WH. global database on body mass index; 2010. *Global Database on Body Mass Index*. 2016.

111. Würtz P, Kangas AJ, Soininen P, et al. Quantitative serum nuclear magnetic resonance metabolomics in large-scale epidemiology: a primer on-omic technologies. *American journal of epidemiology*. 2017;186(9):1084-1096.

112. Yusuf S, Reddy S, Ôunpuu S, et al. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001;104(22):2746-2753.

113. Ye C, Pan Y, Xu X, et al. Pulse wave velocity in elastic and muscular arteries: tracking stability and association with anthropometric and hemodynamic measurements. *Hypertens Res*. 2016;39(11):786-791.

114. Collaboration RVfAS. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors:'establishing normal and reference values'. *European heart journal*. 2010;31(19):2338-2350.

115. Aguado-Sierra J, Davies JE, Hadjiloizou N, et al. Reservoir-wave separation and wave intensity analysis applied to carotid arteries: a hybrid 1D model to understand haemodynamics. *Conf Proc IEEE Eng Med Biol Soc*. 2008;2008:1381-4.

116. Wilkinson IB, McEniery CM, Schillaci G, et al. ARTERY Society guidelines for validation of non-invasive haemodynamic measurement devices: Part 1, arterial pulse wave velocity. *Artery Res*. 2010;4(2):34-40.

117. Ryder JR, Pankratz ND, Dengel DR, et al. Heritability of Vascular Structure and Function: A Parent–Child Study. *Journal of the American Heart Association*. 2017;6(2):e004757.